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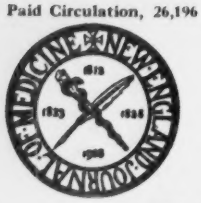

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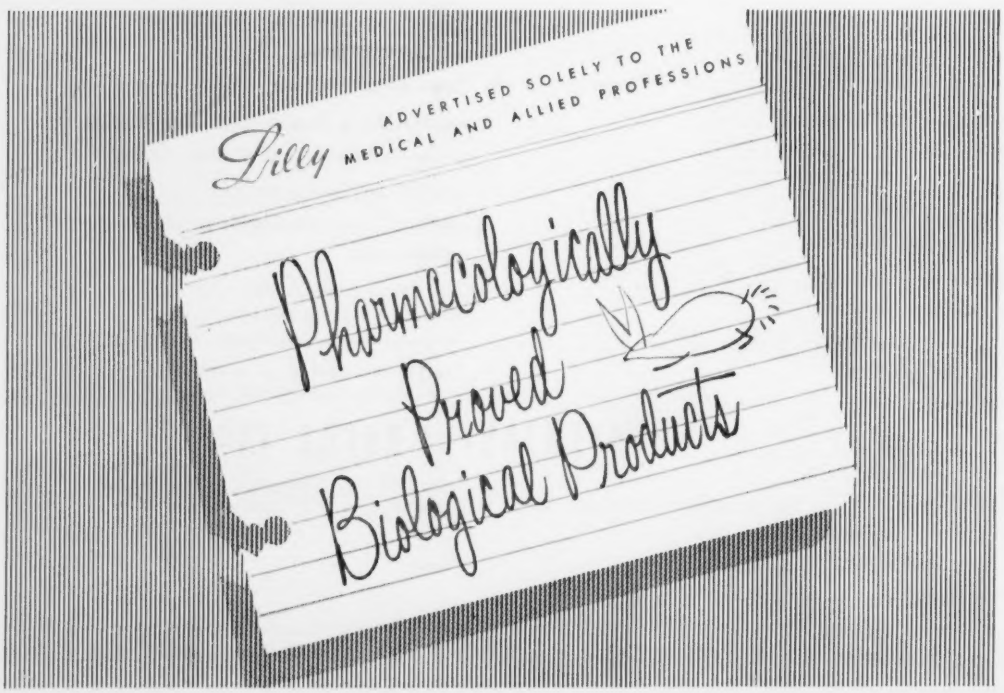

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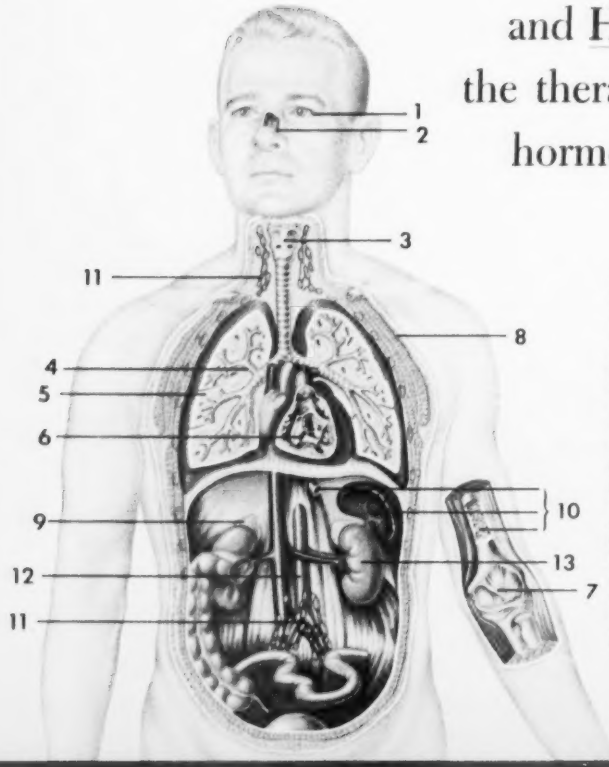

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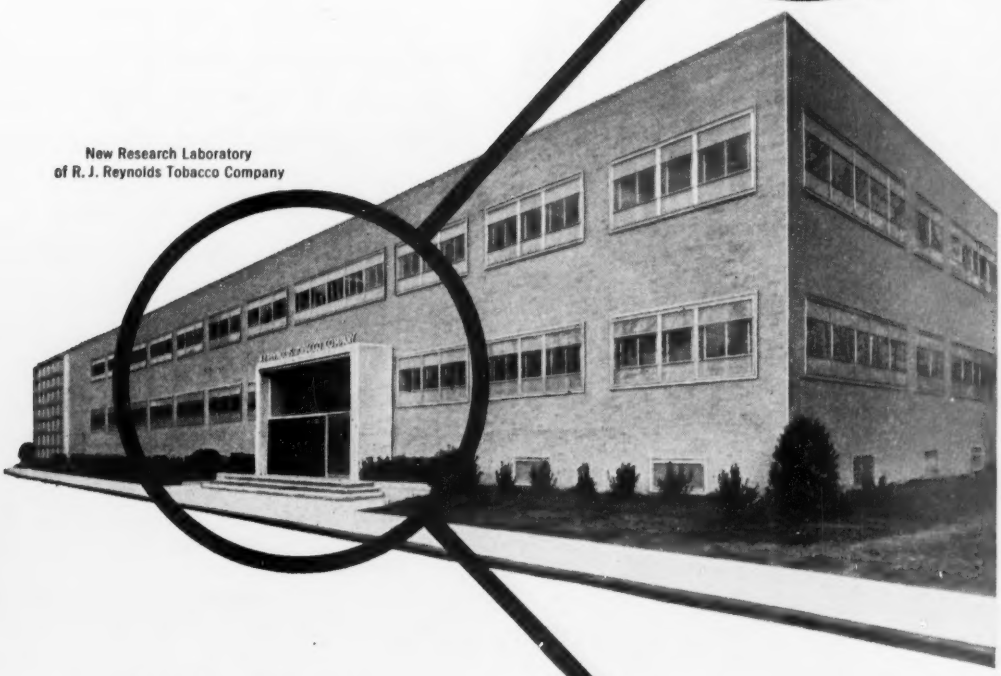

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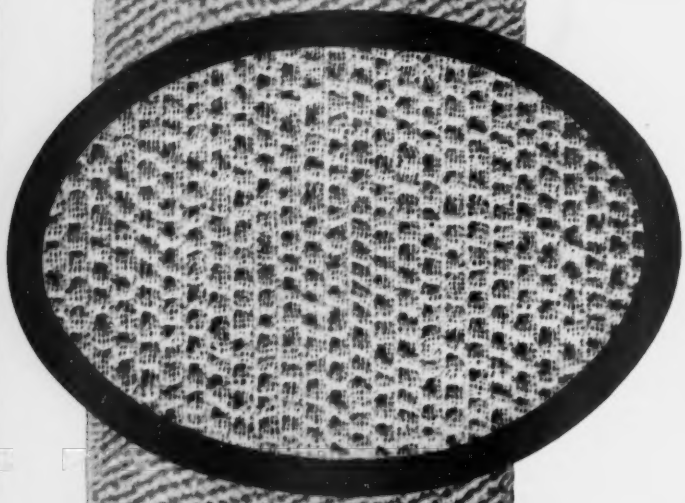

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References Cited

a. *J.A.M.A.*, Vol. 103, 1934, p. 318
b. *J.A.M.A.*, Vol. 135, 1947, p. 417

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Volume 248 JUNE 18, 1953 Number 25

THE SHATTUCK LECTURE

TWENTIETH-CENTURY CHANGES IN THE TREATMENT OF SEPTIC INFECTIONS*

SIR ALEXANDER FLEMING, F.R.C.P., F.R.C.S., F.R.S.†

LONDON, ENGLAND

MICROBIOLOGY started with Louis Pasteur — a chemist. He drifted into microbiology through his work on alcoholic fermentation. He confirmed that alcoholic fermentation was due to a living micro-organism, a yeast, and he found that when the alcoholic fermentation went wrong other organisms were present. This gave him the interest in microbes. Later, he became interested in the microbes of disease.

After Pasteur's time bacteriology was largely medical for many years, but recently the interest in microbes has become much more general and the industrial possibilities of these lowly organisms have become recognized. Microbiology is now important in many industries, and in this expansion of microbiology chemists have played a large part. Chemistry is a significant branch of modern microbiology. Pasteur, a chemist, became a microbiologist and microbiologists are becoming chemists.

It is now just fifty years since I began studying medicine. I was fortunate in my choice of a medical school. There are eleven undergraduate schools in London, and I chose St. Mary's Hospital. It was not then the most famous school in London, but why I was fortunate was that at the same time I went there as a student, Almroth Wright came as the teacher of bacteriology. Almroth Wright was a great man; immediately after I qualified I entered his laboratory, and I was with him until he died a few years ago. I am indeed proud that my name should be associated with his in the name of the institute in which we worked together for so long.

In that fifty years I have seen many changes in the treatment of bacterial disease. When I began working in Wright's laboratory, vaccine therapy was in its infancy. Prophylactic vaccines had been used against typhoid and some other diseases, but the idea of treating infections with vaccines was new and at that time it created just about as much excitement as the antibiotics have in recent years. Workers from all parts of the world came to learn about the methods of making and using the vaccines, and I remember that in the first six months I was in the laboratory we had workers from Canada, the United States, Germany, France, South Africa and other places. Vaccine therapy was useful in many infections, but unfortunately it lent itself to charlatanry and in certain places it was seriously abused and fell into disrepute.

At the time it was the only direct method of combating bacterial infection in the human body.

The next great advance was Ehrlich's introduction of Salvarsan. From the time of Lister it was known that chemicals could kill bacteria and that by the use of these chemicals bacteria could be killed on the surface of the body. Many unsuccessful attempts had been made to use these antiseptic chemicals to destroy bacteria *inside* the body. Ehrlich's ideal was a chemical that in a single dose would overwhelm the infecting bacteria and get rid of the infection. His great discovery of Salvarsan hardly did this, but it revolutionized the treatment of syphilis and a few other diseases, and what was even more important, it showed that there was hope of finding chemicals that could deal with other bacterial diseases. After Salvarsan, however, in spite of an enormous amount of work, there was really little advance in the chemotherapy of bacterial disease until recent times.

World War I was a great stimulus to the study of septic infections. Sepsis in surgical wounds was then, by the introduction of aseptic methods, much less common than it had formerly been, but the fighting in France brought a spate of infected wounds and there were no known effective methods of dealing with them. These gunshot wounds were infected with soil and contaminated clothing that had been driven in and by contaminated skin.

I should like to spend a little time on the infected gunshot wound illustrated by studies made in Wright's laboratory in Boulogne. This was situated

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 21, 1953.

†Hunterian professor and Arris and Gale Lecturer, Royal College of Surgeons; professor of bacteriology and chief, Wright–Fleming Institute for Microbiology, St. Mary's Hospital Medical School; professor emeritus of bacteriology, University of London.

in the Casino (now no more), and that hospital was later taken over by the Harvard Unit when I had the pleasure of working with Roger Lee, Harvey Cushing, Elliott Cutler and many other delightful people.

Figure 1 illustrates diagrammatically a wound freshly inflicted and one in which the infection has grown out and become established. In the freshly

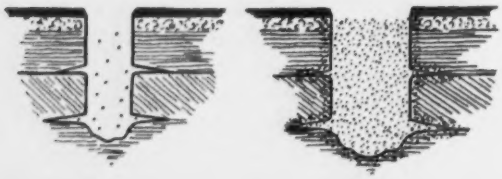

FIGURE 1. *Diagrams of a Wound Shortly after Infliction* (A) *and* (B) *after Infection Has Become Established (the Dots in the Cavity in* A *and in and around the Cavity in* B *Represent Microbes).*

inflicted wound the bacteria (represented by dots) lie in the cavity of the wound, which of course is irregular in shape. It might be imagined that it would be possible to sterilize such a wound by the application of antiseptic chemicals, but with the antiseptics in use it was seldom found to be possible.

I have attempted to imitate a wound in which the infection is limited to the cavity, by means of a tube such as that depicted in Figure 2, which has several small processes drawn out to represent the diverticula that exist in all serious recently inflicted gunshot wounds. In such a tube is placed serum that has been implanted with feces, giving a fair imitation of the primary infection of a wound. After this had been incubated so that the infection might spread throughout the whole tube, I tried to sterilize it with some of the antiseptic in common use. The procedure adopted was to pour out the contents and wash the tube three or four times with the antiseptic solution by filling the tube with it and emptying it out again. Then the tube was filled with the antiseptic solution and left for twenty minutes, after which the antiseptic was poured out and replaced by the serum. The tube was then incubated for twenty-four hours. The result was that there was no change in the flora of the tube on the second day. The next day I "dressed" it in the same way, but left the antiseptic in the tube for an hour. This had no effect. The next day the antiseptic was left in the tube for three hours, but it likewise had no effect. Then the antiseptic was allowed to remain in the tube for twenty-four hours, after which it was emptied out and replaced by serum and the tube incubated as before. Films made of the contents of the tubes (Fig. 2) demonstrated practically no difference between the tube dressed with physiologic saline solution and those in which antiseptic solutions were used. This clearly indicates that it is impossible to sterilize a wound with an antiseptic, even if it is possible to keep the solution in the wound for a long time without dilution, and even if the walls of the wound are not infected. I have carried out the same experiment with brilliant-green and flavine, and found them equally unsuccessful.

When the infection had become established the microbes not only had grown out throughout the

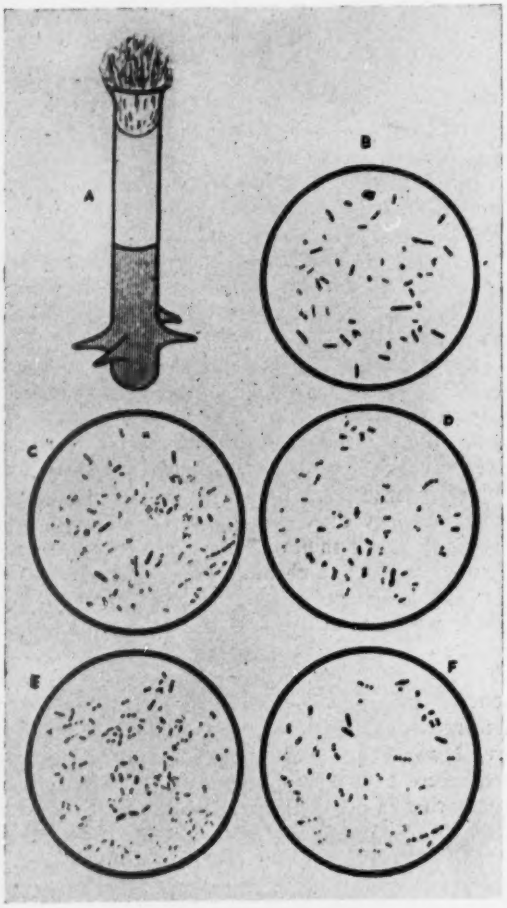

FIGURE 2. *Microscopical Appearance of the Serum in an Artificial Wound* (A), *"Dressed" for Several Days with Physiologic Saline Solution* (B), *5 Per Cent Saline Solution* (C), *Eusol* (D), *Dakin's Solution* (E) *and 1:40 Solution of Carbolic Acid* (F).

whole cavity of the wound but also had penetrated into the walls of the wound for a considerable depth. I tried to imitate such a wound by placing a ball of infected asbestos wool, about the size of a pea, in a test tube, and I then attempted to sterilize it by filling the tube with Dakin's solution, which was

changed at intervals during twenty-four hours. Then the Dakin's fluid was emptied out, and the tube filled with serum and incubated. The tube treated with Dakin's solution gave as good a growth as the control tube that had been treated with physiologic saline solution, and, on examining the growth under the microscope, I found no change in the original flora.

The infected wound exudes a more or less purulent fluid. This consists of a serous fluid and cells, chiefly polymorphonuclear leukocytes. Both the

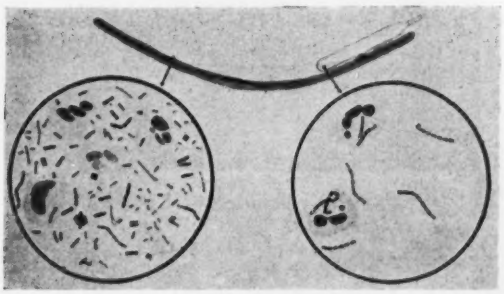

FIGURE 3. *Microscopical Appearance of Smears from Outside and Inside the Lymph Leech.*

fluid and the cells may have an influence on the growth of bacteria. The alkalinity of the fluid may make a considerable difference to the growth of Welch's bacillus, the chief cause of gas gangrene. This organism grows poorly in serum of normal alkalinity and in fact will not grow out at all unless the inoculum is very large, but if the alkalinity is reduced it will grow out freely.

Patients with an acute septic infection have a much enhanced antitryptic power in the serum, and this acts as a nonspecific immunizing process, since most bacteria grow much better in a serum with a low antitryptic power.

A septic wound contains leukocytes, some of which are destroyed, and these liberate into the fluid trypsin that reduces the antitryptic power of the fluid, which is thus made a better culture medium. The fluid in the cavity of a wound has a lower antitryptic power than that in the walls — indeed it may actually be tryptic.

In a simple experiment devised by Wright a tube, which he called a "lymph leech," was made from a test tube. This was placed with its side aperture on the surface of a septic wound that had just been dressed. By withdrawing the piston of the syringe he induced a slight negative pressure, which caused clear fluid from the walls of the wound to exude into the tube. The tube was left in position overnight, and smears were made from the fluid in the tube and from the general surface of the wound. The bacterial flora in the wound was quite varied, but in the "leech" there was nothing to be seen but streptococci (Fig. 3).

Wright divided the wound bacteria into two groups: serophytes, which would grow in "uncorrupted" fluid; and serosaprophytes, which would grow only when the fluid was "corrupted" by broken-down pus cells and other contaminants.

Simple Methods of Determining Leukocytic Function

Polymorphonuclear leukocytes, which constitute the bulk of the cells in the pus, can be studied for emigration, phagocytosis and bactericidal power. The first two can be seen by the simple examination of the cells of fresh pus on the warm stage of a microscope. It is often easier, however, to use the polymorphonuclear leukocytes of blood.

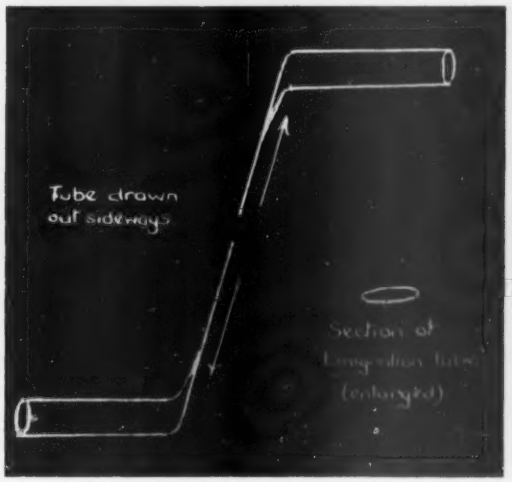

FIGURE 4. *Method of Making Emigration Tubes.*

Wright devised what he called an "emigration tube," which he made by heating a glass tube and then turning over the ends so that they were roughly parallel, and drawing a capillary at right angles to the end-pieces, which acted as handles. In this way the capillary was flat (Fig. 4).

Blood from the finger is run into the tube; one end is sealed, and the tube is put in the incubator in the upright position. The leukocytes are distributed, of course, in the corpuscular layer, but most of them are near the top. The blood clots, and the leukocytes emigrate up the fibrin network of the plasma clot and the glass walls for a considerable distance. This can be observed directly under the microscope, or the clot can be blown out onto a slide and stained. If bacteria are introduced into

the blood they may grow out into small colonies, and then the leukocytes are attracted and attempt to destroy the colonies (Fig. 5).

Another easy method of observing leukocytic emigration is to make a grease ring on a slide and fill it with blood from the finger. The slide is then

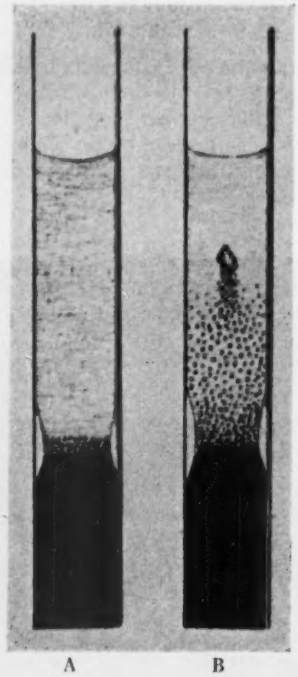

FIGURE 5. *Emigration Tube, Showing Emigration Beginning* (A) *and a Later Stage* (B), *with Leukocytes Attacking a Colony of Streptococci.*

incubated in a moist chamber. After half an hour the clot is thrown off, and the slide is washed under the tap and stained. The floor of the cell is found to be covered with leukocytes that have emigrated from the blood clot, and many of these show irregular forms (Fig. 6).

The slide-cell method constitutes an excellent way of demonstrating the bactericidal power of leukocytes. The apparatus consists of two microscope slides separated by narrow strips of paper about 0.17 mm. thick (Fig. 7). Defibrinated blood, with its full complement of leukocytes and the same blood from which the leukocytes have been removed are infected with staphylococci and run into these cells. The blood with leukocytes kills off 90 to 95 per cent of the cocci, but this bactericidal power is completely absent in the blood from which the leukocytes have been eliminated (Fig. 8).

The leukocytes in pus from a septic wound can be shown to be bactericidal by a simple experiment. A small drop of fresh pus is put on an agar plate, and a coverslip applied. There will be no growth of bacteria in the pus, but a few colonies will appear

FIGURE 6. *Motile Forms of Leukocytes.*

around the drop where some bacteria have been squeezed away from the cells by the weight of the coverslip. If, however, the pus cells are killed by

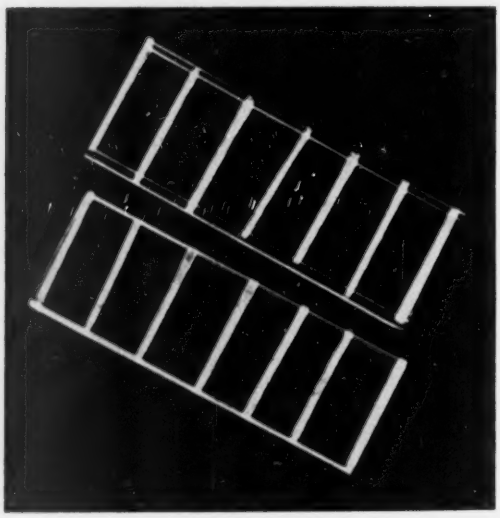

FIGURE 7. *Slide Cells.*

heat, freezing and thawing, or by chemicals, a copious growth takes place throughout the pus (Fig. 9).

EFFECT OF CHEMICAL ANTISEPTICS ON LEUKOCYTES AND BACTERIA

The slide-cell method is admirable for this study so long as the test bacteria are such that they grow

in blood in easily recognizable colonies. Staphylococci and streptococci are suitable organisms for this purpose. Defibrinated blood is infected with an appropriate number of cocci. Dilutions of the antiseptic are made in saline solution in 25-cu. mm.

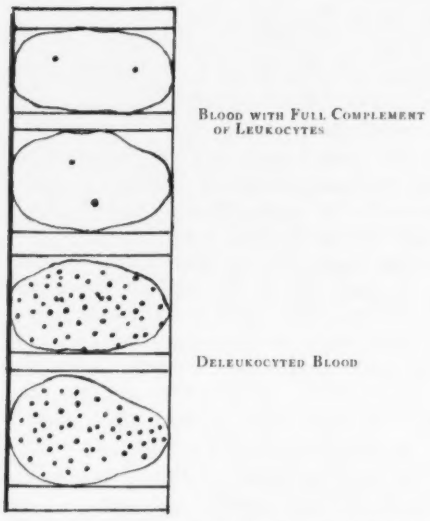

FIGURE 8. *Bactericidal Power of Leukocytes.*

volumes. To each of these is added 25 cu. mm. of the infected blood. The mixtures are run into the slide cells, which are sealed and incubated. If carbolic acid is taken as an example and it is assumed

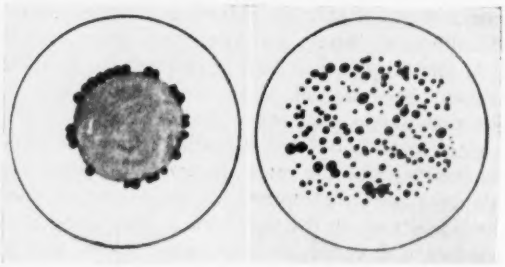

FIGURE 9. *Growth of Bacteria in Fresh Pus* (A) *and in Fresh Pus in Which the Cells Have Been Killed by Heat* (B).

that 100 staphylococci were put in each cell, one finds that the control cell has about 5 colonies and that the weakest carbolic concentration is the same as the control, but when the concentration of carbolic acid reaches 1 in 1000 there will be about 25 colonies and with 1:600 carbolic acid solution there will be 100 colonies (if every coccus grows out). This is because in that concentration the chemical kills all the leukocytes but does not affect the growth of the bacteria (Fig. 10).

This was seen with all the chemical antiseptics until the advent of the sulfonamides. Actually, the first antibacterial substance that I found to have a greater destructive effect on bacteria than on leukocytes tested in this way was crude penicillin, but this did not come into extensive clinical use until after the beginning of the sulfonamide era.

After World War I various chemicals were recommended for introduction into the blood stream with the object of directly destroying infecting bacteria.

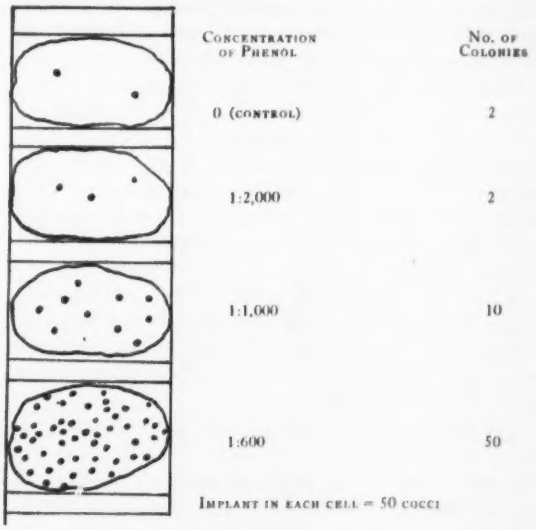

FIGURE 10. *Effect of Phenol on the Bactericidal Power of Blood.*

Among these were Mercurochrome and acriflavine. These drugs were more poisonous to leukocytes than they were to bacteria so that there was little surprise when they failed to justify the claims made for them.

The next great advance was the appearance of the sulfonamides, beginning with Prontosil in the early 'thirties. Until this time only drugs of the Salvarsan series were effective in killing bacteria inside the body, and they had only a limited scope, not touching the common infections of the human body. Investigators were beginning to despair of finding a chemotherapeutic substance that would be effective against the common septic infections. Prontosil was shown to have a powerful curative action on infections with the hemolytic streptococcus but how it acted seemed somewhat of a mystery, for in vitro it had little effect on this organism. Soon, however, it was shown that its curative action was

due to a splitting of sulfanilimide from the Prontosil molecule in the body, and this made the treatment easier and more rational.

Sulfanilamide affected the hemolytic streptococcus, the gonococcus and the meningococcus, and it could deal with many colon-bacillus infections of the urinary tract, although it was not strong enough to affect staphylococcal or pneumococcal infections. However, the chemists busied themselves changing the sulfanilamide molecule and brought forth sulfapyridine, which could cope with pneumococcal infections. This created a great stir, for pneumonia was a disease that affected the general populace, and the chemists further improved matters by producing sulfathiazole, which not only did all that sulfanilamide or sulfapyridine could do but also was powerful enough to affect some staphylococcal infections. Since then there have been many new sulfonamides for which various advantages are claimed.

Then came the antibiotic era, ushered in by penicillin. I had described penicillin in 1929, when it was a crude fluid quite unsuitable for injection into the body but one that appeared to have some of the properties of the ideal chemotherapeutic agent. The crude liquor could be diluted at most up to a thousand times and still stop the growth of staphylococcus, and yet it seemed to be no more toxic to leukocytes or animals than the original culture medium. Now that pure penicillin has been produced, I know that in the culture fluid I worked with in those days, there was a concentration of penicillin of about only 1:200,000.

The antibiotic had to be purified and concentrated before it could be used as a chemotherapeutic agent. This was done by the brilliant work of Florey and his associates at Oxford. They concentrated it about a thousand times and found means of ridding it of certain pyrogens before they demonstrated its extraordinary curative properties. It was far from pure, — in fact, it was only about 1 or 2 per cent pure, — but it was therapeutically active and it was nontoxic.

Florey brought all his information on the preparation of penicillin over to America, and improvements in the culture of the mold and in the preparation of the drug were first made by Coghill and his associates at the Northern Regional Laboratory at Peoria, Illinois, and later by the large pharmaceutical manufacturers.

Penicillin, even in the crude form in which it was first manufactured, was something better than had been imagined possible. On infections by sensitive microbes, doses containing as little as 10 mg. were effective, whereas doses more than a hundred times as much as the curative dose were in no way toxic to the normal man. It is true that sometimes one encountered a sensitive person who suffered from urticaria or some other minor complaint after a dose of penicillin, but it approached close to the ideal chemotherapeutic substance in that it was effective and there was no fear of an overdose.

With penicillin the question was not how much could be given with safety but how little would be effective.

This was different from the two useful chemotherapeutic substances that had gone before. The Salvarsan products were definitely toxic unless the dose was carefully controlled and the sulfonamides, although less toxic, were certainly not without danger when the ordinary dose was exceeded.

Also, the results of penicillin could be dramatic. I remember the first patient I ever treated after Florey's team had concentrated it. He had a streptococcal meningitis on which the sulfonamides had no effect. He was so ill that for two days when I arrived at the hospital in the morning I expected to find that he had died in the night. I got some penicillin from Florey and gave it intramuscularly. There was some improvement, but since examination of the cerebrospinal fluid showed a low concentration of penicillin, I introduced some into the spinal cord — the first time it had been done. Thereafter, recovery was rapid. That one result was enough to convince anyone of the efficacy of the drug, but that is only one of many.

At last there was a drug that could be given with impunity and that conquered, very rapidly, many of the most common infections although it was clear from the beginning that there were many other infections against which it was powerless.

The purification of penicillin and its use in chemotherapy happened in the midst of war when the septic wound was a most serious problem. The first patients treated were infected with the common organisms of sepsis, staphylococci and streptococci, and it was also shown to be effective against the organisms of gas gangrene. This made it appear to be invaluable for Army purposes, and later when it was manufactured in bulk it justified itself in the treatment not only of septic wounds but also of lobar pneumonia and other diseases. This is not the place to go into detail regarding the use of penicillin but perhaps the most spectacular success was in the treatment of venereal disease — another condition important to the military. It was found that gonorrhea was cured in twenty-four hours, and in most cases a week's treatment cured syphilis — usually without fear of toxic reactions. This meant an enormous saving of manpower to the armies.

At first, owing to scarcity of the drug, the dosage was arranged to achieve the maximum benefit from the minimum amount of penicillin. This necessitated injections every three hours day and night, which was disliked by both the patient who received the injections and the attendant who had to give them. As the supply situation improved, larger doses were given at longer intervals, but this was not a complete

answer to the problem because a tenfold increase in the dose little more than doubled the time that penicillin could be found in the blood.

Figure 11 shows approximately the time penicillin can be detected in the blood after doses of varying sizes.

The next improvement was to introduce penicillin in such a form that it formed a depot from which it was only slowly absorbed. This was first done by Romansky, who incorporated penicillin in oil and beeswax. When this was injected in a dose of 300,000 units the drug persisted in the blood for twenty-four hours so that the treatment could be carried out with single daily injections. There were, however, technical difficulties that made people welcome the advent of procaine penicillin.

In the early days of penicillin the manufactured product was very impure and somtimes gave considerable pain on injection. To counteract this procaine was often mixed with the penicillin solution in the syringes. Sometimes, it was noticed that a precipitate formed, but this did not affect the potency of the penicillin.

Later it was found that procaine formed with penicillin a salt that was only slightly soluble in water and, when introduced into the body as a suspension, was slowly dissociated. As with the oil-wax mixture, a dose of 300,000 units persisted in the blood for twenty-four hours. It was found also that if aluminum monostearate was added to the oily suspension of procaine penicillin the dissociation was further delayed so that a single dose would last for three days. Procaine penicillin made the treatment much easier for both doctor and patient, but the slow absorption meant that there was never a high concentration in the blood. To overcome this drawback, soluble sodium penicillin was often given in combination with the relatively insoluble procaine salt. This ensured a high initial concentration in the body, together with a long-continued action.

More recently other salts of penicillin have appeared.

Diethylaminoethyl-ester hydroiodide of benzyl penicillin is a sparingly soluble salt that forms a depot like the procaine salt. Its peculiarity is that it appears to have an affinity for the inflamed lung and appears in much higher concentration in the sputum. This should be of advantage in the treatment of lung conditions.

Still more recently another insoluble salt, dibenzylethylenediamine di-penicillin G, has appeared. It is stated that an injection of 600,000 units of this salt is followed by the appearance of measurable quantities of penicillin in the blood over a period of fourteen days. Of course, there is never a high level, but the amount is sufficient to deal with sensitive organisms. This may in certain circumstances be of great value, but it must be remembered that for the last seven days or more the blood levels may not be high enough to inhibit the growth of anything but the most sensitive of organisms. There may be a grave danger of breeding out of resistant strains by exposure to nonlethal concentrations.

Another salt, allylmercaptomethyl penicillin, or penicillin O, is said to cut down materially the incidence of allergic manifestations following the administration of penicillin so that patients who have previously had allergic manifestations can have penicillin treatment.

The success of penicillin led to an intensive search for new antibiotics. It seemed inconceivable that penicillin, which was discovered fortuitously, should be the best. Since penicillin had been made by a mold, it was among the molds that the search began.

Actually, I had done this in a small way in the 'thirties by testing any stray mold that appeared in the laboratory. I was not an expert in molds, and there was not, at that time, any indication that penicillin could be extracted satisfactorily from the culture fluid or that it would be such an extraordinarily potent chemotherapeutic substance. My efforts consequently came to nothing although I found that several molds produced antibacterial substances none, however, as potent as penicillin.

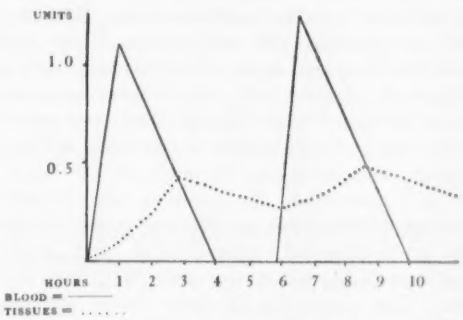

FIGURE 11. *Levels of Penicillin in Blood and Tissues.*

The molds have been found to produce many antibiotics, but none so far have been of therapeutic value.

Then the search extended up and down the scale from the flowering plants to the bacteria. With every class of plant antibiotics have been discovered. Nothing useful has come from the flowering plants and the higher fungi, but from the actinomycetes and the bacteria a number of valuable antibiotics have been discovered.

It was the work of Waksman that directed attention to the actinomycetes and especially to the streptomycetes, which form a branch of the family. For many years before penicillin appeared he had been studying this group of organisms, of which he had a considerable collection. These were investigated for the production of antibiotics, a number were found, but they were not useful in medicine. Later, Waksman, in conjunction with Schatz and

Bugie, described streptomycin,—a product of a recently isolated strain of *Streptomyces griseus*,—which had a powerful action on many gram-negative bacilli that were resistant to penicillin. Subsequently it was found to have a powerful action on the tubercle bacillus, and it is for its antituberculosis action that streptomycin is particularly important. It was relatively nontoxic, but in doses of 2 gm. a day for more than a week it had a specific toxic action on the eighth nerve, especially the vestibular portion. Apart from this, the chief drawback was the rapidity with which resistant forms of bacteria appeared.

However, streptomycin has been of immense service in many tuberculous conditions and still remains the most important chemotherapeutic agent in the treatment of tuberculosis. It has given hope for the sufferer from tuberculous meningitis in the same way that penicillin gave hope to the patient with subacute bacterial endocarditis.

Three other antibiotics derived from streptomycetes have proved their worth—namely, chloramphenicol, aureomycin and terramycin. They are called the broad-spectrum antibiotics because of the wide range of infection with which they can deal. By means of these drugs typhoid fever and other salmonella infection, typhus fever and other rickettsial diseases and infections by some of the larger viruses are controlled. In addition, the broad-spectrum antibiotics have an effective action on the common staphylococcal, streptococcal and pneumococcal infections, which are also dealt with by penicillin. The properties of these drugs are too well known to need comment, but I must refer to the blood dyscrasias that have, in a small number of cases, followed the use of chloramphenicol. It is obvious that some care must be exercised in the dosage of this drug and that the blood picture must be watched.

Other antibiotics are erythromycin and magnamycin, which are still more or less on clinical trial.

Bacterial Antibiotics

From different bacterial cultures many antibiotics have been isolated, and several of these are now on the market.

Tyrothricin is noteworthy as the only antibiotic in use before the penicillin era. It was described by Dubos in 1939. It is too toxic for systemic use but it can be used locally. It acts on the gram-positive organisms especially, and it seems likely that it would have been used extensively for septic wounds in the war except that penicillin, which was more powerful and without toxicity, appeared.

Bacitracin, another bacterial antibiotic, has somewhat the same spectrum as penicillin but it is to some extent nephrotoxic so that care with the dosage must be taken. An interesting feature of bacitracin is that it seems, like penicillin, to have a synergic action.

Polymyxin has quite a different spectrum. It acts on the gram-negative organisms. Like bacitracin, it has some nephrotoxic action, but it has proved useful in some infections, especially those due to *Proteus vulgaris* and *Pseudomonas aeruginosa*, which are resistant to other antibiotics.

The search goes on, and doubtless more will be discovered. Before an antibiotic appears on sale many things have to happen:

In the first place, a biologist has to discover that one micro-organism produces something that antagonizes other microbes. He has to develop culture mediums in which this substance is freely produced, and he has to investigate the antibiotic "spectrum"—that is, he must ascertain which organisms are sensitive and which are insensitive.

Secondly, a chemist has to purify the active substance as far as he can. If he succeeds in purifying it he tries to discover its formula and, if possible, to synthesize it.

Thirdly, a pharmacologist has to study the action of the purified product. He investigates its absorption and excretion. Especially, he must study its toxicity—not only the acute toxicity after a single dose but also the possibility or organic damage after a long-continued course of smaller doses. (Many antibiotics that at first seemed nontoxic were found to cause serious damage to the kidneys or other organs after continued administration.) Then he sees the effect of the drug on experimental infections in animals.

Fourthly, if the antibiotic passes the tests of the pharmacologist, the physician sees whether it can cure disease in man. He has from the biologist a list of the sensitive organisms. He has from the pharmacologist the dose that in animals is effective and also the information on absorption and excretion so that he knows whether he has to give it orally or parenterally. He must observe the rate of excretion and level of the drug in the blood so that he may know how frequently to repeat the dose, and he has to adjust the dose so that a therapeutic level is maintained in the blood for a sufficient time.

Fifthly, if, from the observations of the physician, the drug appears valuable, the pharmaceutical manufacturer must devise methods of production on a large scale. With penicillin this was difficult, since so many new problems were encountered, but now problems connected with the growth of the organism in large containers are better understood and progress is much more rapid. It was four or five years after penicillin was first purified before satisfactory large-scale manufacturing methods were devised, but only nine months elapsed between the discovery of terramycin and its issue to the public.

Finally, someone gives the antibiotic a name. Penicillin was so named because it was elaborated by a penicillium, and in general the name of the genus or species of the organism producing the antibiotic is indicated in the name allotted to it.

What of the Future?

The search for new antibiotics will go on, and new ones will appear. These antibiotics are substances made by living organisms that have a chemical constitution different from anything the organic chemists regarded as antibacterial substances. Most of the antibiotics that have been discovered are useless therapeutically, and most of them have not been chemically analyzed. Each one whose formula has been defined gives to the chemists a new antibacterial chemical combination. Doubtless, they will work on these new molecules, and by altering them as Ehrlich did the molecule of atoxyl, or the more recent workers the molecule of sulfanilamide, produce new compounds with antibacterial powers and lessened toxicity. Because some of the bacteria have the power of making themselves resistant to all the antibiotics, it is essential that drugs should not be abused. That is difficult in these days of newspaper publicity.

Summary

I have tried to discuss briefly fifty years of the treatment of the common bacterial infections. I have not mentioned the enormous surgical advances in this connection, since that is outside my sphere.

I started with vaccine therapy progressing to Ehrlich's beginning of chemotherapy, and then to modern sulfonamide and antibiotic treatment. It has been stimulating to take part in this revolution and to see what misery is spared many sufferers in this age. And this progress is far from being at the end.

So far I have only mentioned antibiotics in connection with the treatment of human disease. Of course, they have the same effect in the treatment of the same infections in animals, but they are now used extensively in quite another aspect of animal husbandry. If a small amount of antibiotic is incorporated in the feeding stuff of young poultry or pigs, they appear to grow faster, put on more weight and get ready for the market more quickly. This is important economically, and perhaps in the near future more antibiotics will be used for animal feeding than for medicinal purposes.

MORTALITY OF PERSONS WITH PHOTOFLUOROGRAMS SUGGESTIVE OF CARDIOVASCULAR DISEASE*

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COLUMBUS, GEORGIA

THE advent of photofluorography has made possible the radiologic screening of the chests of millions of persons each year. Although this method has been largely applied to tuberculosis case finding, many cardiovascular abnormalities have also been detected by this procedure. Since diseases of the cardiovascular system are responsible for an increasingly large number of deaths each year, efforts have been made to determine the potential usefulness of chest photofluorography as a means of detecting persons with cardiovascular disease, with the assumption that patients found in routine surveys might be benefited more by appropriate treatment than those seeking medical care because of symptoms. This assumption is based on the premise that persons who are most likely to die of cardiovascular diseases may in some significant degree be selected from the general survey population by the abnormal appearance of their cardiovascular shadows as revealed by chest photofluorograms. Although it may seem obvious that a cardiovascular shadow of abnormal size or shape is likely to be associated with a fairly serious prognosis, it may be of interest to report the degree to which a community-wide survey was able to select persons from this ambulant population who later died of causes related to the cardiovascular system.

Although the Muscogee County Tuberculosis Study was primarily designed to investigate the epidemiology of tuberculosis, certain of its data have a bearing on the study of cardiovascular diseases suspected from the examination of chest photofluorograms. As reported previously,[1,2] the original data were derived from a community-wide tuberculosis and venereal-disease survey conducted in Muscogee County, Georgia, in May and June, 1946. In the course of this survey, 43,429 residents‡ of the county over the age of fifteen years had 70-mm. photofluorograms of the chest and serologic tests for syphilis. Because the medical officer in charge of the survey was interested in cardiovascular diseases, somewhat more effort than was usual at that time was made both in recording possible cardiovascular abnormalities noted in the interpretations of the survey films and in recalling those with such interpretations for re-examination.

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‡"Resident" in this paper is defined as a person giving a Muscogee County address at the time of the survey examination.

These persons were sent a mimeographed letter requesting that they return to the clinic for further examination — those not responding to the first letter were sent a second notice. As a result of these two letters, 80 per cent of this group were re-examined in the clinic. A few more subsequently returned to the clinic for other reasons, so that by January 1, 1950, 83.9 per cent of the group had returned for re-examination.

The clinic examination was of necessity somewhat cursory, being designed primarily to eliminate as many false-positive results as possible before these persons were referred to their own physicians for further study and treatment. It consisted of a brief historical review of the cardiovascular system, physical examination of the chest, blood-pressure determination in the sitting position, and fluoroscopic study of the chest. Full-sized chest films in various positions were taken occasionally. In addition, the results of the serologic tests for syphilis made in this survey were available to the clinician. If the impression from the clinic examination agreed with the survey impression of cardiovascular disease, the person was urged to seek further medical advice from his own physician, to whom the findings were reported.

Table 1. *Evidence of Cardiovascular Disease among the Surveyed Population over Fifteen Years of Age, by Race and Age.*

Age Group	Surveyed Population	Chest Photofluorograms Classified as Suggestive of Cardiovascular Disease	
		no.	percentage
Whites:			
15–24	6,806	13	0.2
25–34	6,898	10	0.1
35–44	5,569	8	0.1
45–54	3,293	16	0.5
55–64	1,644	29	1.8
Over 65	674	36	5.3
Totals	24,884	112	
Average			0.46
Negroes:			
15–24	5,528	27	0.5
25–34	5,156	35	0.7
35–44	4,085	121	3.0
45–54	2,344	196	8.4
55–64	924	131	14.2
Over 65	508	117	23.0
Totals	18,545	627	
Average			3.38

Although no further follow-up efforts were devoted to these cases, the data from the master index file of the tuberculosis study is applicable to an analysis of the mortality in this group. Every person examined in the 1946 survey is represented by a card in this file, on which the results of the survey examinations are recorded. Death certificates for all deaths occurring in Muscogee County have been matched against the master index file, and the date and cause of death are recorded.

The study procedures provided no means of measuring emigration from the county or of obtaining information on deaths occurring outside the county during the period covered by this analysis (July 1, 1946, to January 1, 1950). However, there is no known reason to believe that the emigration of persons with cardiovascular disease has been different from that of the rest of the population or that an appreciable number of residents have died outside the county. Thus, for the three and a half-year period after the survey, it is possible to determine the minimum mortality experienced by 739 persons whose cardiovascular shadows on the survey photofluorograms were considered abnormal, and to compare it with that experienced by 42,690 persons whose survey films were classified as giving no significant evidence of cardiovascular disease.

Prevalence of Cardiovascular Abnormalities Suspected from the Survey Photofluorograms

Among the persons examined in the 1946 survey there were 43,429 over the age of fifteen years who gave Muscogee County addresses. Of these, 739, or 1.70 per cent, had chest photofluorograms interpreted as indicative of cardiovascular abnormalities. Marked differences in the prevalence of such abnormalities were noted between whites and Negroes, the Negroes showing much higher rates at all ages (Table 1). Males showed a generally higher prevalence of recorded cardiovascular abnormalities among both race groups and at all ages. However, the difference between the sexes in this respect did not seem sufficient to require a further subdivision of the data. The proportion of persons among the white population whose survey films indicated possible cardiovascular disease was approximately 0.1 per cent in the group from fifteen to forty-five years of age. This ratio then rose slowly until the age of sixty-five, and reached a peak of 5.3 per cent for the group over that age. The proportion among the Negroes was approximately 0.6 per cent from fifteen to thirty-five, with a subsequent progressive rise to a level of 23.0 per cent among the group over sixty-five. Only 1 out of 36 white persons over the age of fifty-five was classified as suspected of having cardiovascular

Table 2. *Types of Cardiovascular Abnormality Suspected.*

Type of Abnormality	Totals	Whites		Negroes	
		males	females	males	females
Situs inversus	9	—	4	1	4
Congenital heart disease	4	2	—	—	2
Rheumatic heart disease	22	3	5	6	8
Cardiovascular syphilis	82	7	—	49	26
Hypertensive disease	288	13	12	127	136
Pericardial disease	1	—	—	1	—
Arteriosclerotic heart disease	7	4	1	1	1
Thyroid heart disease	1	1	—	—	—
Pulmonary congestion	2	—	1	—	1
Suspected heart disease	20	1	2	8	9
Widened aorta only	88	2	1	51	34
Totals	524	33	26	244	221

disease; among the Negroes over fifty-five, 1 out of every 6 was placed in this category.

Although the clinic examinations were too cursory to yield reliable diagnostic data, the types of cardiovascular lesion suspected by the clinician among the persons who returned for examination may be of interest. These impressions (Table 2) show that the greater frequency of abnormalities suspected in Negroes from the 70-mm. survey films could be ascribed largely to hypertensive disease.* Cardiovascular syphilis also appeared to be much more common among the Negroes, as did the category of "widened aorta only," for which no etiologic impression was recorded. These findings are in accord with the observations of others that both hypertension and cardiovascular syphilis are more common among Negroes than among whites.[3-5]

Mortality

Among the 739 persons whose survey photofluorograms were considered to indicate cardiovascular disease, 116 (15.7 per cent) are known to have died in the three and a half years after the survey (July 1, 1946, to January 1, 1950). Table 3 shows the deaths among this group by race and broad age groups. There was an increase in the mortality with age, from about 6 per cent in the group fifteen to thirty-four years old to nearly 20 per cent among those over fifty-five years of age. There was no appreciable difference between the two races in this respect, except for the apparently greater mortality among the whites aged thirty-five to fifty-four than among the Negroes. However, with the small numbers involved the significance of this difference is dubious.

The fact that nearly a sixth of the persons recalled because of suspected cardiovascular disease were dead three and a half years later is quite striking, especially if it is recalled that these persons were all ambulant and, almost without exception, had no disabling symptoms at the time of the survey examination. The mortality rate among this group thus becomes even more impressive when compared to the deaths that occurred in the same period among persons whose survey photofluorograms were classified as negative for cardiovascular disease. These data are also shown in Table 3 by race and by broad age groups. For the whites, the rates were fifteen times higher among those suspected of having cardiovascular disease than among those with negative survey findings; for the Negroes, those with survey films classified as indicating suspected cardiovascular disease showed a death rate seven times higher than those with films classified as negative. The differences were most marked in the group fifteen to thirty-five years of age, but even among persons over fifty-five, the death rates for those with films suggesting cardiovascular disease were about three times as high as the rates for those with films classified as being negative for cardiovascular abnormalities.

Table 3. *Total Deaths among Residents Surveyed.*

Age in 1946	Survey Negative for Cardiovascular Disease			Suspected Cardiovascular Disease on Survey		
	Survey Population	Total Deaths		Survey Population	Total Deaths	
yr.		no.	%		no.	%
Whites:						
15–34	13,681	35	0.25	23	1	4.3
35–54	8,838	102	1.15	24	5	20.8
Over 55	2,253	149	6.61	65	14	21.5
Totals	24,772	286		112	20	
Averages			1.15			17.9
Negroes:						
15–34	10,622	98	0.92	62	4	6.5
35–54	6,112	193	3.15	317	44	13.9
Over 55	1,184	84	7.08	248	48	19.4
Totals	17,918	375		627	96	
Averages			2.09			15.3

If the deaths registered as due to renocardiovascular diseases† are studied among the group of persons recalled because of suspected cardiovascular disease, the pattern is similar to that noted for all deaths (Table 4). The reason for the similarity in pattern is that 81 per cent of deaths among this group were reported as due to renocardiovascular disease, a fact that tends to confirm the specificity of the survey-film impression of cardiovascular disease. Within three and a half

*Hypertension was defined in this study as a systolic blood pressure greater than 140 and a diastolic pressure greater than 90. Blood pressures were recorded on the right arm, with the subject seated. Systolic pressures were defined as the level at which sounds were first audible, and diastolic pressures as the level at which the sounds became muffled.

†This classification includes the following causes of death (*International List of the Causes of Death*, fifth revision):

30d	Syphilis — aneurysm of aorta
30e	Other syphilis of circulatory system
83	Intracranial lesions of vascular origin
92	Chronic affections of valves and endocardium
93	Diseases of myocardium
94	Diseases of coronary arteries and angina pectoris
95	Other diseases of the heart
96	Aneurysm
97	Arteriosclerosis
102	High blood pressure
131	Chronic nephritis
132	Nephritis, unspecified (ten years of age and over)
157e	Congenital malformations of the heart
157f	Congenital malformations of the cardiovascular system.

years nearly 13 per cent of this group of persons died of causes related to the renocardiovascular group of diseases.

With the deaths limited to those from these causes, the comparison with those whose chest photofluorograms were considered negative for cardiovascular disease becomes even more striking than when the comparison is made on the basis of all deaths. The mortality among whites from renocardiovascular causes for the post-survey period of three and a half years was thirty-one times as great among those classified as having cardiovascular disease as among those with films considered to be negative; the ratio for the Negroes was 14. Again the difference between the "cardiovascular suspects" and the "negatives" was greatest in the youngest age group, but was still considerable even among those over fifty-five.

Table 4. *Deaths from Renocardiovascular Causes.*

Age in 1946	Survey Negative for Cardiovascular Disease			Suspected Cardiovascular Disease on Survey		
	survey population	renocardiovascular deaths		survey population	renocardiovascular deaths	
yr.		no.	%		no.	%
Whites:						
15–34	13,681	3	0.02	23	1	4.3
35–54	8,838	36	0.40	24	5	20.8
Over 55	2,253	95	4.21	65	13	20.0
Totals	24,772	134		112	19	
Averages			0.54			17.0
Negroes:						
15–34	10,622	11	0.10	62	2	3.2
35–54	6,112	91	1.48	317	38	12.0
Over 55	1,184	50	4.21	248	35	14.1
Totals	17,918	152		627	75	
Averages			0.84			12.0

These findings afford strong evidence for the validity of the premise that changes in routine chest photofluorograms interpreted as being suggestive of cardiovascular disease can afford a method for selecting from the general population a small group of persons among whom the risk of dying from diseases related to the cardiovascular system is much greater than that of the rest of the population. Whether or not this group of persons who are thus labeled as having "suspected cardiovascular disease" can be benefited by treatment is another matter, but at least it appears that chest x-ray surveys for cardiovascular disease can fulfill one purpose of a screening examination—namely, to identify among the total surveyed population a relatively small group of persons whose subsequent mortality experience shows that they are in need of further remedial or preventive measures.

Discussion

Because the majority of the persons whose films were interpreted as suggestive of cardiovascular disease were re-examined in the clinic and because these persons were advised to consult their own physicians (to whom a copy of the survey and clinic findings was sent), it is possible that the opinion of the clinic physician influenced the diagnoses subsequently made. This in turn could have influenced the cause of death noted on the death certificates and could thus explain in considerable measure the agreement between the survey-film impressions and the death-certificate diagnosis. To explore this possibility, a study was made of the records of persons labeled "cardiovascular suspects" as a result of the survey who were later certified to have died of renocardiovascular diseases, to determine how often the physician who received a report of the clinic and survey findings later signed the death certificate. This study showed that in only 10 per cent of such cases was the death certificate signed by the same physician who received a report from the clinic. In a slightly higher proportion, the clinic records did not definitely specify whether or not a report had been sent. However, even if it is assumed that in all such cases a report was sent to the signer of the death certificate, it would have been possible for the survey examination to have influenced the certified cause of death in only a fifth of this group. Consequently, it does not appear likely that the opinion of the clinic physician had an influence on final certification of the cause of death in a sufficiently large number of cases to have accounted for much of the agreement between the survey film impression and the certified cause of death. In any event, the diagnostic label assigned by the clinic physician could have had no effect on the fact of subsequent mortality, and it has been shown that total mortality among the group with "suspected cardiovascular disease" was considerably greater than that among those classified as "negative for cardiovascular disease."

The fact has already been noted (Table 1) that Negroes at each age group showed a much higher frequency of chest x-ray findings considered to be suggestive of cardiovascular disease than the whites did. A possible explanation of this differ-

ence is the distribution of various types of heart disease among the two races. Both syphilis and hypertension tend to produce cardiac hypertrophy and changes in the aortic silhouette—changes that are often readily noted in the posteroanterior chest x-ray film. Since both these diseases are more common among Negroes than among whites, it might reasonably be expected that radiographic screening methods would cause more Negroes than whites to be classified as cardiovascular suspects.

However, it is possible that still another factor bearing on the increased prevalence among Negroes of cardiovascular disease suspected from the chest photofluorograms is that Negroes may live longer than whites after cardiovascular changes detectable on the posteroanterior chest film develop. Such cases would then tend to accumulate among the Negro population to a greater extent than among the white. That this may be so is suggested by the mortality rates among persons with films showing "suspected cardiovascular disease" (Tables 3 and 4). The rates are a little higher among whites than among Negroes, the difference being most marked in the group thirty-five to fifty-four years of age. However, the numbers involved are small, and the difference between whites and Negroes is not significant in the usual statistical sense.

Further evidence bearing on this point can be obtained by study of the interval between the survey and the time of death for cardiovascular suspects dying from renocardiovascular disease (Table 5). Among the white suspects who died of renocardiovascular causes, 63 per cent died less than twelve months after the survey, as compared with only 25 per cent of the Negro suspects in the same period. This difference is statistically significant. Even when the proportion of suspects dying within a year of the survey is studied in relation to age, it is found for each broad age group that the mortality among whites exceeds that among Negroes, although the difference between the two races in this respect becomes less marked with increasing age. Consequently, for the population under observation in this study, it appears that Negroes live longer than whites after radiographic evidence of cardiovascular disease develops. This finding could account for part of the difference observed between the white and Negro populations in the proportion of persons with chest photofluorograms considered suggestive of cardiovascular disease.

It should be noted that it is not known how many persons were examined in the survey because of chest symptoms except that all persons were ambulant. If the white population whose chest photofluorograms were classified as suggestive of cardiovascular disease had contained a higher proportion of persons with symptoms due to cardiovascular disease than that among Negroes, the differences in early post-survey mortality might be explained by this factor, since persons with symptoms might be expected to die sooner than those who are asymptomatic. Although such specific selection in the survey sample does not seem altogether likely, it must be admitted that there is no direct evidence on this point.

Under the conditions of this community x-ray survey, it has been shown that it was possible to select a group of persons among whom the subsequent mortality was considerable and that most of the deaths were attributed to renocardiovascular disease. Conversely, the proportion of persons subsequently dying from this cause was much lower among those whose survey photofluorograms were considered to be negative for cardiovascular disease. Among the whites, only 12 per cent of the post-survey deaths from renocardiovascular disease occurred among the group classified by the survey-film reader as having suspected cardiovascular disease; among the Negroes, the proportion was 33 per cent. In this respect, the survey procedure failed by a considerable margin to identify all the persons whose subsequent deaths showed them to be extremely important in a consideration of the heart-disease problem in this community.

Although perfection is not to be expected in the use of chest x-ray screening for the detection of cardiovascular diseases, the work of Rutstein et al.[6] shows that the yield of significant cardiac disease can be increased considerably if the survey films are interpreted by physicians with specialized training. This is a factor that merits serious consideration in the planning of screening programs for the detection of cardiovascular disease. However, the

TABLE 5. *Interval between Survey and Death among Persons with Survey Photofluorograms Classified as Showing Cardiovascular Disease.*

Interval after July 1, 1946	Total Deaths		Renocardiovascular Disease	
	Number	Cumulative Percentage	Number	Cumulative Percentage
mo.				
Whites:				
0–5	6	30	6	32
6–11	6	60	6	63
12–17	2	70	1	68
18–23	3	85	3	84
24–29	0	85	0	84
30–35	2	95	2	95
36–41	1	100	1	100
Totals	20		19	
Negroes:				
0–5	13	14	8	11
6–11	13	27	11	25
12–17	14	42	9	37
18–23	24	67	20	64
24–29	8	75	7	73
30–35	10	85	8	84
36–41	14	100	12	100
Totals	96		75	

present study demonstrates that even without such specialized training, a conscientious survey-film reader was able to narrow down the group to be investigated for cardiovascular disease to less than 2 per cent of the surveyed population, and that the group thus selected yielded a fourth of the deaths from renocardiovascular disease occurring within a subsequent period of three and a half years.

It must be admitted that it is not yet known to what extent death and disability can be decreased among ambulant persons whose chest photofluorograms are classified as indicating suspected cardiovascular disease. This study provides no evidence on this point, except for the impression that the advice given at the time of the clinic examination failed to motivate many of the persons examined to return to their own physicians for treatment and follow-up examinations. In any event, the fact still remains that the group of cardiovascular suspects identified in this mass x-ray survey contributed considerably to the problem of renocardiovascular disease in this community as measured by subsequent mortality. Consequently, in the consideration of measures that may be beneficial in reducing the present incidence of death and disability from these diseases, it seems logical to investigate further the potential usefulness of procedures based on chest x-ray screening of the ambulant population.

Summary

In 1946, 70-mm. chest photofluorograms of 43,429 residents of Muscogee County, Georgia, were taken in a community-wide survey. The record system of the Muscogee County Tuberculosis Study made possible the study of the subsequent mortality experienced by this surveyed population.

Of the surveyed population, 1.70 per cent had chest photofluorograms that were interpreted as indicative of cardiovascular abnormalities. The white population contained a smaller proportion of persons so classified than the Negro, and the difference increased markedly with age. Among whites over the age of fifty-five, only 1 out of 36 was classified as a cardiovascular suspect, as compared with 1 out of every 6 Negroes in the same age group.

Nearly a sixth of the persons suspected of having cardiovascular disease were dead three and a half years after the survey. For the whites, the total mortality among those in the category of suspected cardiovascular disease was 15 times that among those labeled as negative for cardiovascular disease; the ratio for Negroes was 7. The mortality rate from renocardiovascular causes among the whites was 31 times as great for those classified as suspected cardiovascular disease as among those considered negative; the ratio for Negroes was 14.

Among the whites suspected of having cardiovascular disease, 63 per cent of the renocardiovascular deaths occurred during the first year after the survey, as compared with only 25 per cent among the Negroes regarded as cardiovascular suspects during the same period. This difference may partially account for the greater proportion of cardiovascular suspects among the Negro population than among the whites.

Under the conditions of this community x-ray survey, it is shown that it is possible, from the appearance of the cardiovascular silhouette on 70-mm. chest photofluorograms, to select a group of persons whose subsequent experience demonstrates that their risk of dying from renocardiovascular causes is very much greater than that of the rest of the surveyed population. The selected group, less than 2 per cent of the surveyed population, yielded nearly a fourth of the renocardiovascular deaths known to have occurred among the surveyed population in the three and a half years after the survey.

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ORAL CORTISONE TREATMENT OF INFANTILE ECZEMA*

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THERE is no doubt that cortisone or adrenocorticotropin (ACTH) often causes spectacular temporary improvement in infantile eczema.[1-5] It is my opinion, however, that these agents when given parenterally and in a hospital, in spite of their great theoretical interest and undoubted temporary favorable action, have little place in the practical over-all management of the disease, for the eczema returns as soon as the treatment is discontinued, and the difficulties of keeping it up over a long period are formidable. The course of the disease is merely interrupted for a short time — it is doubtful if the results are worth the trouble and large expense of hospitalization involved.

Treatment with cortisone by mouth is a different question. If the dosage necessary to relieve the eczema does no harm to the child when continued over long periods, this should be a valuable and practical therapy. If, to control the eczema, doses large enough to cause any side effects whatever are necessary, cortisone should not be used, except perhaps for a short time in critical situations. Short-term therapy with large doses is of little practical value except for periods of extreme emergency; long-term therapy with smaller doses must be used if hormone therapy is to be accepted as a worthwhile adjunct in the treatment of infantile eczema. Dosage is the crux of the whole matter.

To explore the practical possibilities of oral cortisone therapy 18 infants under the age of three years were treated.* Most cases were severe; some patients had done poorly with other usual methods of treatment. Six were under six months of age, 5 between six months and one year, and 7 between one and three years. The duration of treatment was between one and two and a half months for 3 patients, three and six months for 13 patients, and eleven months for 1 patient. Potassium chloride, 0.3 gm. (5 gr.) twice a day, was given to all; antibiotics were not given as a routine, but were used if there was the slightest suspicion of skin or respiratory-tract infection.

It was decided at the outset that not more than 75 mg. of cortisone a day would be given to any patient, on the assumption that at this level of dosage serious side effects would be unlikely. This was adhered to for all except 1 patient. In addition to the use of cortisone, each patient was treated as he would have been if cortisone had not been used. It was found that for patients who responded quickly to cortisone little local treatment was necessary. The cases reported below are classified as follows: Group A, results unsatisfactory (4 cases); Group B, results superior (8 cases); and Group C, results worth while but not superior (6 cases).

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*The cortisone employed was kindly supplied by Merck and Company, Incorporated, Rahway, New Jersey.

CASE REPORTS

Group A

CASE 1. P. O'C., a 6-month-old boy, had severe nummular eczema. He was kept on cortisone, 50 to 75 mg., most of the time for 11 months. He had a number of acute episodes of severe oozing, when serum poured from each lesion, and on one occasion the serum protein was too low to be read on the colorimeter. Cortisone in doses of 75 mg. seemed to help prevent this situation, and probably aided in its control when it did occur. This dosage, however, had no effect on the essential lesions of the disease (Fig. 1).

FIGURE 1. *Appearance of the Patient in Case 1 after Three Weeks Treatment with 75 Mg. of Cortisone by Mouth. The oozing is controlled. The characteristic lesions are otherwise unchanged.*

During a severe exacerbation the patient was admitted to a hospital, and was not under my immediate charge. The ward resident prescribed 100 mg. of cortisone daily (the previous dose had been 75 mg.), which controlled oozing from the lesions very well. Because the eosinophil count dropped but little, the dose was increased to 150 mg. This dosage relieved the eczema temporarily, but an acute potassium deficiency, with characteristic electrocardiographic changes and clinical signs of great severity (stupor and extreme prostration), developed.

Nummular eczema does not respond well to any method of treatment. It has been considered a variant of atopic dermatitis — some think it has nothing to do with allergy. This child had the condition in the most severe degree I have ever seen, and the usual methods of treatment (immunologic and local) had no appreciable effect. Cortisone, in doses of 50 and 75 mg., may have been of some value in that it reduced oozing and kept the lesions relatively dry. It had, however, little or no value as far as the over-all picture of the disease was concerned. Cortisone has been discontinued for several months, and the patient is slowly improving.

Case 2. M. A., a 19-month-old girl, had nummular-type eczema, similar to that in Case 1, only not so extreme. She had been treated by several very competent pediatricians and dermatologists, and had been hospitalized for some weeks, with no benefit whatever. On December 17, 1952, cortisone, in a dosage of 75 mg. daily, was started. On December 24 she was no better. On December 31, when the eczema had not improved cortisone was discontinued.

Figure 2. *Appearance of the Patient in Case 3 on February 11, 1952, Before Treatment.*

Case 3. R. C., a 5-month-old boy, had eczema of a severe erythrodermic type, with marked glandular enlargement and much scaling (Fig. 2). On February 14, 1952, cortisone, 75 mg. daily, was started. Five days later the skin was practically normal, and the dose was cut to 50 mg. daily.

On March 12 examination showed very slight eczema, but coarse hair had begun to grow all over the forehead and on the cheeks (Fig. 3). There was also excessive growth of scalp, eyelash and eyelid hair, and marked rounding of the face. The dosage of cortisone was reduced to 25 mg.

Nine days later there was no change in the hair on the face. Marked recurrence of the eczema was observed (Fig. 4). Cortisone was gradually discontinued.

The results were unsatisfactory. The amount of cortisone necessary to control the eczema (not large doses) produced a typical Cushing syndrome.

By July 30 the excessive hair and rounding of face had gradually lessened, but the eczema had grown steadily worse, so that the patient was in poor shape. There was also complete erythroderma, blue hands and feet, general glandular enlargement, much loss of weight and severe diarrhea. Cortisone was started again, in a dosage of 75 mg. daily.

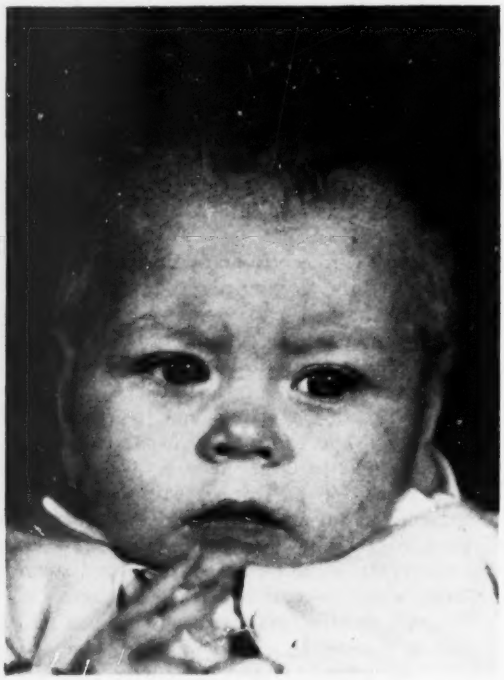

Figure 3. *Appearance of the Patient in Case 3 on March 5, 1952.*

On August 8 he was a different child. Improvement had been spectacular. He had a fine appetite and no diarrhea and was in excellent general condition; the skin was nearly normal.

The patient was kept on cortisone (37.5 to 50 mg.) until December 3. His general condition was good, but there was always a good deal of eczema with this dosage, and the signs of Cushing's syndrome had not entirely disappeared, so that it was thought unwise to raise the dosage. For this particular infant the dosage that would do any appreciable good to the eczema produced undesirable side effects.

Case 4. J. F., a 3-year-old child, had a severe chronic diffuse papular atopic dermatitis, of 2 years' duration. On July 16, 1952, cortisone, 75 mg. daily, was started. In 2 days the eczema was nearly gone.

On August 6 the patient had been free of eczema until 1 week previously, when it recurred in as severe a form as in the beginning. The dosage of 75 mg. of cortisone daily was continued.

A week later, since there was no improvement, the dosage was raised to 87.5 mg. daily. On August 20 the patient was no better. Cortisone was discontinued.

In this case large doses of cortisone would probably have caused a remission. I do not believe, however, that it is at present good practice to give large doses to eczematous children as young as this, except in extreme emergency.

Group B

Case 5. W. D., a 2-3/12-year-old patient, had a severe exacerbation of generalized eczema and hay fever, probably from birch and oak pollen, of about 2 weeks' duration. On May 15, 1951, cortisone, 50 mg. daily, was started. Two weeks later the patient was nearly well. The dose was kept at this level for 2 weeks more and then gradually reduced and the hormone was discontinued.

On June 15 pollination was over. There was no recurrence in 1951.

It is for just such seasonal episodes that cortisone will probably prove to be of most value.

Case 6. L. M., a 2-2/12-year-old girl, suffered from a very severe papular atopic dermatitis that covered the entire body and was probably due to house dust. This was an unusually irritable child. The eczema had interfered with the parents' sleep for months, to such a degree that they were "on the verge of a nervous breakdown."

On January 9, 1952, cortisone, 75 mg. daily, was started. A week later there was no dermatitis and no itching; the patient was practically well. The dosage of cortisone was reduced to 50 mg. and then to 37.5 mg., and she was kept on this dosage until May 21. She was seen on September 23, when she had no eczema whatever but reported several episodes of mild asthma.

Case 7. P. S., a 2-year-old patient, had severe subacute atopic dermatitis involving the arms, face and popliteal spaces of 1 year's duration. On February 27, 1952, cortisone, 50 mg. daily, was started. On March 28 there was no eczema whatever. Cortisone was gradually discontinued. The total duration of treatment was 6 weeks.

Follow-up examination 3 weeks after cortisone had been discontinued showed slight recurrence of no consequence; 5 months later the skin was entirely normal.

Case 8. L. C., a 5-month-old girl, had severe, acute oozing atopic dermatitis, mostly on the face, of 2 months' duration. Cortisone, in a dosage of 50 mg. daily, was started on March 5, 1952. Ten days later the face was nearly normal, and the daily dosage was cut to 37.5 mg.

On March 28 there was a severe recurrence. The face was red and crusted, with some oozing. The dosage of cortisone was increased to 50 mg. a day. Examination on April 18 showed little eczema. The dosage was gradually reduced, and for the next 2 months 25 mg. a day was enough to control the eczema.

At follow-up examination 2 months after cortisone had been discontinued there was no eczema.

Case 9. N. M., a 5-month-old infant, had severe atopic dermatitis of the face (Fig. 5*A*), arms and trunk. On April 2, 1952, cortisone, 50 mg. daily, was started. A week later there was no eczema on the arms and body and only slight eczema on the face (Fig. 5*B*). During the next 3 months the eczema was kept in excellent control with doses of 37.5 mg. or occasionally 50 mg. a day. Cortisone was discontinued on July 30. Follow-up examination on August 27 and October 22 showed no eczema.

Case 10. R. P., a 5-month-old boy, had severe atopic dermatitis of the face and trunk, with much oozing of the face. Cortisone therapy, in a dosage of 50 mg. daily, was started on February 2, 1952. There was not much improvement in 3 days. On February 5 the dosage was increased to 75 mg. a day. By February 11 the skin was entirely clear.

This infant was given cortisone for 5 months. The eczema recurred immediately with any dosage less than 50 mg. He was seen 1 month after cortisone had been discontinued. There was no recurrence.

Case 11. D. W., a 9½-month-old boy, had moderately severe atopic dermatitis of the face, chest, arms and legs (Fig. 6). Cortisone, in a dosage of 75 mg. daily, was started on July 23, 1952. A week later there was practically no eczema (Fig. 7); the dosage was cut to 50 mg. a day.

On August 13 the mother stated that the eczema had returned after 2 days, so that she put the patient back on a dosage of 75 mg. a day. Only slight eczema was apparent. The dosage of cortisone was reduced to 62.5 mg. daily. Two weeks later examination showed no eczema. For the next 4 months the dosage varied between 37.5 and 75 mg. a day. Cortisone was discontinued on November 20. The patient was seen on December 3, when there was slight erythema of the cheeks — no eczema was observed anywhere else.

Case 12. J. D., a 6-month-old infant, had severe erythrodermic eczema, with marked general lymph-node enlargement and blue and cold feet. On October 1, 1952, cortisone, 75 mg. daily, was started. A week later the face was nearly normal

Figure 4. *Appearance of the Patient in Case 3 on March 21, 1952.*

although there was still some eczema on the body. The dosage of 75 mg. was discontinued.

On October 22 there was no eczema and the feet were warm. Enlargement of the lymph nodes had nearly disappeared. The dosage of cortisone was reduced to 62.5 mg. a day for 1 week and then to 50 mg. On November 12 it was noted that there was practically no eczema, and the dosage of cortisone was cut to 37.5 mg. daily.

Examination on December 3 disclosed slight eczema around the neck, probably from rubbing of a snow suit. Dosage of 37.5 mg. a day was continued.

On February 11, 1953, there was very little eczema around the wrists and none elsewhere. Cortisone was gradually discontinued. By March 4, when cortisone had been given for 2 weeks, examination showed very slight eczema, of no moment. The patient's general condition was excellent.

Group C

Case 13. L. K., a 9½-month-old girl, suffered from severe atopic dermatitis, subacute, scattered over the arms, legs, face and trunk.

Cortisone, in a dosage of 75 mg. daily, was started on January 23, 1952. One week later there as no eczema whatever and no

itching. It was found that 75 mg. of cortisone daily was the smallest amount that would do this patient much good. She was kept on this dosage most of the time for 5 months and had no eczema. There were no side effects. Cortisone was discontinued.

On June 25, 3 months after cortisone had been discontinued, there was about 30 per cent recurrence of the eczema.

Case 14. B. L., an 8-month-old infant, had severe generalized atopic dermatitis, with a good deal of scaling, of 3 months' duration.

Cortisone, 75 mg. daily, was started on May 7, 1952. A week later there was 50 per cent improvement. By May 27 the cortisone dosage had been cut to 50 mg. daily. This dosage was continued until July 30, when it was reduced to 25 mg., the drug being discontinued on August 27.

At follow-up examination on September 24, no eczema was apparent. The results were not classified as superior because the response was very slow.

Case 15. F. L., a 3-year-old boy, suffered from unusually severe atopic dermatitis, with excoriated papules all over the body. He was in poor general condition, with intolerable itching.

On May 15, 1952, cortisone was started in a dosage of 75 mg. Six days later there was very little eczema. On May 28 there was no eczema whatever. The dosage of cortisone was reduced to 50 mg. daily, but this proved to be insufficient: on June 13 there was about 75 per cent recurrence. Cortisone in a dosage of 75 mg. was resumed.

Examination on July 2 showed very little eczema; the patient's general condition had improved remarkably; there was little itching. The dosage of cortisone was cut to 50 mg., varying between 25 and 62.5 mg. a day. From this time until November 12, when a little less than half the eczema originally noted was present, cortisone was discontinued. The total duration of treatment was 6 months.

It took 75 mg. a day of cortisone to keep this boy entirely free from eczema, but since this dosage caused a slight growth of hair on the face, it was thought best to keep the dermatitis under fair control with a moderate amount (75 mg.) rather than to try to keep him entirely free from it with a larger dosage.

Case 16. M. P., a 1-year-old child, had severe erythrodermic eczema, with marked general lymph-node enlargement, a great deal of large scaling and very blue feet. On October 1, 1952 cortisone, 75 mg. daily, was started. Seventeen days later the legs and arms were nearly free from eczema; the feet were still blue, and the face about as before. The drug was continued in a dosage of 75 mg.

On October 22 the patient had practically no eczema. The feet were warm, and the lymph-node enlargement had nearly disappeared. Nutrition was excellent. The patient felt well and was a different child. The dosage of cortisone was reduced to 62.5 mg. daily for 1 week and then to 50 mg.

Examination on November 12 showed practically no eczema. The feet were no longer blue, and the lymph-node enlargement had disappeared. The dosage of cortisone was cut to 25 mg. daily. However, this proved to be insufficient since on December 23 marked recurrence of the eczema on the face, back and arms was noted. The dosage of 50 mg. was resumed.

On December 31 the patient was about the same. The dosage was increased to 62.5 mg. and continued at this level until January 29, 1953, and then reduced to 50 mg., since examination showed very slight eczema.

When last seen on February 18 the patient had been taking 37.5 mg. of cortisone daily for the last 4 days. There was very slight eczema. Cortisone was continued in a dosage of 37.5 mg. a day.

Case 17. E. B., a 2-10/12-year-old child, had severe scattered atopic dermatitis all over the trunk, extremities and face. On December 10, 1952, cortisone was started in a dosage of 75 mg. daily. One week later the eczema was nearly gone, so that the dosage was cut to 62.5 mg. daily. The dosage was further reduced — to 50 mg. a day on December 31, when the patient was about the same, and to 37.5 mg. daily on January 21, 1953, when only slight eczema was observed.

On February 4, when marked recurrence of the eczema showed that this dosage was not sufficient, cortisone was resumed in a

A B

Figure 5. *Appearance of the Patient in Case 9 before* (A) *and after One Week's Treatment* (B).

daily dosage of 50 mg., which was continued. Examination on February 18 showed very little eczema. On March 10 the patient was about the same. The dosage of 50 mg. daily was continued.

CASE 18. D. G., a 10-month-old infant, had the erythrodermic type of eczema (partial only), with a great deal of seborrheic scaling, particularly on the face and scalp, of 5 months' duration. On July 23, 1952, cortisone was started in a dosage of 75 mg. daily. One week later the skin was nearly normal.

For the next 4 months the daily dosage varied between 75 and 50 mg. The body and face remained entirely free of eczema, but there was a large area around the neck, extending up into the scalp in the occipital region and behind the ears, that persisted in spite of continued cortisone and local treatment (75 mg.). Cortisone was discontinued on December 3.

FIGURE 6. *Appearance of the Patient in Case 11, before Treatment.*

DISCUSSION

It has been said that the dosage of cortisone for infants and children is entirely independent of the size of the patient — that they need, and should take, the same dosage as adults, and that the severity of the disease is the sole criterion of dosage. It is certainly true that infants need and tolerate enormously larger doses in proportion to their weight than adults, but I do not believe that they tolerate the larger doses (150 to 300 mg.) often given to adults. If infantile eczema is to be treated with cortisone at all, it must be treated with a dosage that does no harm. There is justification for unlimited dosage in such disorders as pemphigus, lupus, periarteritis nodosa and status asthmaticus; there is no justification for large doses in such a disease as infantile eczema. If the eczema is entirely controlled with 75 mg. or less, cortisone should be continued at this level; if it is not entirely controlled with that amount, it is my opinion that it is best not to try for a complete "cure" with larger dosage. The best general principle is to use the smallest possible dosage that will keep the eczema under moderately good control and will keep the child comfortable and the mother satisfied.

The optimum dosage seems to vary not so much according to the severity of the disease as according to the patient — the occurrence of side effects also probably depends to a large extent on the individual case. In Case 13, for example, the eczema was not nearly so severe as it was in some of the others reported, and yet the patient needed 75 mg. of cortisone over a long period if the dermatitis was to be controlled, and this dosage over a long period produced no side effects. In Case 2, on the other hand, well marked Cushing's syndrome developed while the patient was taking 50 mg. a day. Case 8, although she had severe facial eczema, did well for a large part of her course on 25 mg. a day (this is distinctly unusual).

FIGURE 7. *Appearance of the Patient in Case 11, after One Week's Treatment.*

It is best to start with 75 mg., and as soon as the eczema is controlled, to do a downward titration, with reduction of 12.5 mg. each time to determine

what daily dose is necessary for the patient. There may be an appreciable difference in response between 37.5 and 50 mg., or between 37.5 and 25 mg.

The general condition is excellent while the infant is taking cortisone. He eats well, sleeps well and feels well and, I suspect, may be a little euphoric. His flesh is firm and hard, and if he has been poorly nourished, as some of these patients are, in a short time he is a vigorous, healthy-appearing baby in a good state of nutrition. The problem of growth in relation to treatment with cortisone requires further long-term investigation. I have seen no evidence so far that cortisone in the dosage used has seriously interfered with growth or bony maturation.

One of the pitfalls of treatment with cortisone is that while it is being used one is likely to forget that it is symptomatic treatment only, and that if the disease is really to be conquered, search for the cause must be carried out just as it was before the days of cortisone. Cortisone is merely an addition to the generally accepted methods of treatment; it in no sense supplants them, or changes the allergic status of the child.

The presence of skin or respiratory infection is not necessarily a contraindication to the use of cortisone provided the child is seen frequently and an antibiotic is given. If during the course of treatment a surgical operation is necessary, it is of the utmost importance that the dose be increased by at least 50 per cent before and for several days after the operation.

When cortisone is discontinued this should not be done abruptly. It has been my practice to discontinue the hormone by giving 25 mg. a day for four days and then 25 mg. every other day for a week. I have seen no adverse symptoms from discontinuance.

Summary and Conclusions

Eighteen eczematous children ranging in age from four and a half months to three years of age, were treated with orally administered cortisone. The duration of treatment varied between one and a half and eleven months, the average being three to six months. The results of treatment were superior in 8 cases, worth while in 6 and unsatisfactory in 4. The only immediate adverse side effects were the production of Cushing's syndrome in 1 patient, and potassium deficiency in another when the dose was too large (150 mg.).

Cortisone given orally is a valuable addition to local and immunologic treatment for some infants with severe eczema.

It is possible to continue cortisone treatment for several months without apparent harm to the child.

The dosage should be kept as small as possible; except for extremely critical situations it is probably best not to use over 75 mg. a day. No evidence can be offered, however, that it might not be possible to use somewhat larger doses with advantage.

Treatment with cortisone is symptomatic only, for the purpose of tiding the child over a difficult period, and during treatment dietetic and environmental control and local therapy must not be neglected.

Although no harm is apparent in most infants treated for relatively long periods with moderate doses of cortisone, this treatment should be used for severe cases only, and for as short a time as possible, to relieve an immediate, distressing situation. An entire cure is not expected, and it is better to maintain the eczema under reasonably good control with moderate doses than to suppress it entirely with large doses.

I am indebted to Dr. Charles A. Janeway, professor of pediatrics at Harvard Medical School, for his helpful suggestions and constructive criticism.

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SOURCES OF UPPER GASTROINTESTINAL HEMORRHAGE IN CIRRHOTIC PATIENTS WITH ESOPHAGEAL VARICES*

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WHEN the patient who is hospitalized because of massive hemorrhage from the upper gastrointestinal tract is found to have the clinical signs of portal cirrhosis, the diagnosis of bleeding esophageal varices must often be assumed. Personal errors based on this assumption, particularly when emergency therapy was recommended, led to a routine study to discover how often patients with proved cirrhosis have other lesions of the upper gastrointestinal tract that may be responsible for hemorrhage.

TABLE 1. *Methods of Examination.*

GROUP	NO. OF PATIENTS	X-RAY STUDY OF UPPER GASTROINTESTINAL TRACT	ESOPHAGOSCOPIC EXAMINATION	GASTROSCOPIC EXAMINATION	SURGICAL EXPLORATION	AUTOPSY
		NO. OF PATIENTS	NO. OF PATIENTS	NO. OF PATIENTS	NO. OF PATIENTS	NO. OF PATIENTS
History of hemorrhage	59	56	59	27	25	15
No history of hemorrhage ...	91	91	91	13	14	6

MATERIAL AND METHODS

A hundred and fifty patients with cirrhosis were studied. There were 30 women, 6 Negroes, 4 Puerto Ricans and 1 Japanese in the group. The numbers of patients per age decade from the second through the eighth were, respectively, 2, 18, 46, 45, 25, 10 and 4.

All patients had histologic proof of cirrhosis — 146 by needle biopsy, 1 by peritoneoscopic biopsy, and 3 by autopsy examination only. There were 134 cases of portal cirrhosis, 12 of postnecrotic cirrhosis, and 4 of cirrhosis due to infection with *Schistosoma mansoni*.

Studies carried out in the effort to detect potential bleeding sites are outlined in Table 1.

FINDINGS

Esophagoscopic examination, which was performed in all patients, revealed esophageal varices in 95. There was a history of serious hemorrhage from the upper gastrointestinal tract in 59 patients, 47 of whom were found to have esophageal varices. Among 91 patients without a history of hemorrhage, there were 48 cases of esophageal varices.

The material presented in Table 2 is largely self-explanatory. Thirty-nine per cent of the patients with a history of hemorrhage had one or more lesions of the upper gastrointestinal tract in addition to varices that could have been responsible for the hemorrhage. Among those without a history of hemorrhage, 20 per cent had other potential bleeding sites. Other lesions were associated in 22 per cent of the 95 patients with varices. Duodenal ulcer was the commonest disease accompanying varices, having been found in 10 per cent of all patients. Gastric ulcer, hiatus hernia and esophagitis were each demonstrated in 7 cases. The 2 cases of Mallory–Weiss syndrome,[1, 2] were diagnosed on clinical grounds alone.

TABLE 2. *Correlation between History of Serious Hemorrhage, Presence of Esophageal Varices and Presence of Other Potential Bleeding Lesions.*

LESION	HISTORY OF HEMORRHAGE		NO HISTORY OF HEMORRHAGE	
	NO. OF CASES	CASES WITH VARICES	NO. OF CASES	CASES WITH VARICES
Duodenal ulcer	9	6	6	3
Gastric varices.....	5	5	1	1
Hiatus hernia.....	5	3	2	2
Hypertrophic gastritis	3	2	2	0
Erosive gastritis	3	2	0	0
Gastric ulcer	1	0	6	3
Mallory-Weiss syndrome	2	0	0	0
Esophagitis.....	2	1	5	4
Prolapse of gastric mucosa ...	0	0	1	1
Rendu-Osler-Weber disease ..	1	0	0	0
Carcinoma of pancreas invading stomach	0	0	1	0
Carcinoma of esophagus	1	1	0	0
Polyp of esophagus	1	1	0	0
Leukemic infiltration of stomach	0	0	1	0
Esophageal diverticulum	1	1	0	0
Total lesions.....	34	22	25	14
Total patients with lesions .	23	15	18	8
Total patients in group	59	47	91	48

Twenty-one patients died during investigation, and all were studied at autopsy. The periods of observation from patient to patient were most variable, and, of course, many patients came under study because of a complication of cirrhosis or of some other disease; therefore, this figure is not of significance in connection with the prognosis of

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cirrhosis. Sixteen of the patients who died were found to have had varices, and 15 had had a history of hemorrhage.

Eleven of the 21 patients died of hemorrhage, and in 7 cases the hemorrhage was determined, on the basis of endoscopic study and autopsy, to have been due to esophageal varices. Two patients died of hemorrhage from acute erosive gastritis, 1 of hemorrhage from duodenal ulcer, and 1 of hemorrhage from leukemic infiltration of the stomach.

Discussion

Although this was a routine study, the patients were of necessity examined and treated according to the individual exigencies presented, and indications for diagnostic investigation varied considerably. In all cases study of the esophagus and duodenum was considered complete, but the fact that only 27 per cent of the stomachs were examined gastroscopically makes it likely that cases of gastritis, gastric varices and gastric ulcer were overlooked.

Only 3 cases of erosive gastritis were encountered, and these were diagnosed gastroscopically during active hemorrhage. This important disease, one must note, is an ephemeral one. Large areas of the superficial layer of the gastric mucosa may suddenly exfoliate, to permit massive hemorrhage, but it heals just as quickly. The potential seriousness of the resulting hemorrhage has been well documented,[3-5] and in the present series 2 patients died of this cause. It would be a mistake to consider the 3 cases mentioned here to be an indication of incidence. In view of the facts that this form of erosive gastritis can be detected only during the brief period of its acute activity and that it may be initiated by portal hypertension, all the patients studied may be considered to have been susceptible. The suggestion of others[6, 7] that gastroduodenal ulcer may be more common in cirrhotic patients than in the population as a whole received support in this study.

In our opinion these data indicate the need for endoscopic and x-ray study[8] in each patient with a diagnosis of cirrhosis before the dread complication of hemorrhage supervenes. Knowledge of all potential bleeding lesions is necessary for adequate therapy of hemorrhage.

Conclusion

The observations presented imply an important warning against immediate assumption that esophageal varices are at fault when the cirrhotic patient presents himself with massive hemorrhage. An argument emerges for thorough diagnostic study under the circumstances. Wider utilization of emergency surgical procedures to halt hemorrhage from esophageal varices makes it increasingly important that the actual source of hemorrhage be determined. Forearming oneself with knowledge obtained simply by endoscopic and radiologic study of the upper gastrointestinal tract in each cirrhotic patient permits rational treatment in the event of complication.

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MEDICAL PROGRESS

Report of an unusual case with a brief discussion of the role of the thymus in the disease

MALIGNANT THYMOMA IN MYASTHENIA GRAVIS*

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THE first modern clinical and pathological descriptions of the disease that was to be named myasthenia gravis[1] were made by Wilks,[2] Erb[3] and Goldflam.[4] Only a few years later, in 1901, Weigert[5] first described the association of a thymic tumor with myasthenia.

By 1917 Bell[6] had collected 56 autopsied cases of myasthenia, with a benign tumor of the thymus in 10 and a generalized enlargement of the gland in 17 others. Thus, approximately 50 per cent of the patients had thymic abnormalities. In 1936 Norris[7] reported similar figures among 80 cases collected to that date in which the thymus had been examined. Blalock,[8] several years later, added 30 cases in which 18 abnormalities of the thymus were found. Castleman and Norris,[9] in an extensive review of the subject in 1949, reported 35 cases of myasthenia in the experience of the Massachusetts General Hospital and gathered from the literature all those in which the thymus had been examined either at operation or post mortem. In the 330 cases thus described there were 97 thymomas, giving an incidence of gross tumor of about 30 per cent. An almost identical incidence has recently been reported in a smaller series from Sweden.[10] However, since it is generally the unusual or interesting case that is reported in the literature, the figure of 15 per cent given by Seybold et al.[11] is probably more nearly representative of the actual clinical incidence. Most authors now agree with Keynes[12] that in the patients without thymomas the glands are by and large grossly normal and, in contrast to the earlier accounts, not beyond the normal limits for size, which varies considerably even within the same age groups.

The incidence of myasthenia in patients with thymomas has been said to approach 100 per cent,[13, 14] although Seybold and his associates[11] have given a figure of 75 per cent. Castleman and Norris[9] observed that tumors in association with myasthenia are more likely to develop in men over forty years of age, whereas female patients tend to manifest myasthenia at an earlier age and in the absence of a thymic neoplasm.

That a benign solitary thymoma associated with myasthenia may be found in aberrant positions has recently been emphasized. Such cases have been described within the parenchyma of the lung,[15] in the pleural space[16] and in the neck[10] Ectopic thymomas may thus simulate bronchiogenic or metastatic carcinoma.

Although Bell[6] believed that only benign tumors of the thymus were associated with myasthenia, numerous cases of so-called malignant thymomas have been reported in that condition.[14, 17-20] It has in fact been estimated[9] that about 10 per cent of all thymomas grow beyond the capsule of the gland and invade other intrathoracic structures by direct extension. They can also be surgically seeded, and in an unusual case reported by Derow et al.,[20] there was apparent bronchiogenic spread. No cases have been recorded in which true metastases to distant lymph nodes or organs were found.

The following case is unusual because, when biopsy was performed, the widespread infiltration of the tumor within the chest and its extension into the axilla mistakenly suggested lymph-node metastasis and confused the diagnosis. However, penetration through the diaphragm into the abdomen was subsequently found at post-mortem examination.

CASE REPORT

J. H. (M. G. H. 756443), a 43 year-old landscape gardener, first entered the Massachusetts General Hospital in November, 1951, because of muscular weakness. Two years previously, while at work, he had suddenly felt weak and fallen to the ground. He did not lose consciousness and recovered completely in a few moments. A few days later, however, he began to notice some drooping of the eyelids and blurring of vision. During the course of the next month diplopia, difficulty in chewing, dysphagia, weakness of voice and finally weakness of the arms successively developed. All symptoms were absent on awakening and became progressively worse during the course of the day. He lost about 50 pounds during the first 6 months of his illness.

A diagnosis of myasthenia gravis had been made at another hospital in August, 1949. X-ray films of the chest taken at that time revealed a questionable tumor mass, which on needle biopsy was said to have demonstrated a metastatic transitional-cell carcinoma of the pleura. The patient received 2400 r to the upper chest and after this improved a good deal and was well regulated on 4 prostigmine tablets (15 mg.) daily. In September, 1950, the symptoms returned and he received an additional 6000 r to the chest through anterior and posterior portals. He again improved, although he increased his prostigmine dosage to 7 tablets a day. In the spring of 1951 the patient suffered another relapse and was seen by Dr. Henry R. Viets, who confirmed the diagnosis of myasthenia gravis and increased the prostigmine dosage to 20 tablets daily. This was followed by moderate improvement, and because of previous excellent responses to x-ray therapy it was decided to re-evaluate the thoracic lesion with a view toward thymectomy.

Physical examination revealed a thin but well developed man in no acute distress. The skin over the chest showed the effects of the x-ray therapy. A large, firm, nontender lymph node was felt in the right axilla. The trachea deviated to the right, and

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the right hemithorax expanded poorly. There was dullness at the right base, where the breath sounds were diminished but had a grating quality. The heart was not enlarged, and no murmurs or rubs were heard. The liver edge was palpated 2 cm. below the costal margin, and was smooth and nontender. No other abdominal organs or masses were palpable. There was marked weakness of the facial muscles, with moderate ptosis but no diplopia. The voice was hoarse, and the gag reflex diminished. The shoulder muscles showed great weakness, which increased with use. The rest of the neurologic examination was normal.

The pulse was 88, and the respirations were 22 and unlabored. The blood pressure was 110/65.

Routine laboratory studies were normal. X-ray examination of the chest demonstrated marked pleural thickening, chiefly over the right lower lobe, and a mediastinal mass with hilar adenopathy.

Because it was decided that the films of the chest indicated a widespread malignant neoplasm, plans for thymectomy were abandoned and the patient was given a third course of x-ray therapy. After he had received 2000 r, severe nausea and vomiting caused discontinuation of treatment. There was no change in the size of the lesion or in the symptoms.

In December, the patient was readmitted to the hospital in acute respiratory distress, for which he was placed in a respirator. Aside from this, physical examination was the same as previously. On a regime of frequent oral and subcutaneous administration of prostigmine, he steadily improved, and at discharge 2 months later he was able to get along without a respirator and subsequently to return to light work. He was taking 27 prostigmine tablets daily at this time.

In April, 1952, he was once again admitted to the hospital in acute respiratory distress, which had slowly developed over the preceding week. He was again placed in a respirator. He had an elevated white-cell count and some fever; in addition to subcutaneous prostigmine, he was treated with antibiotics, with an excellent response. Biopsy of a lymph node in the right axilla revealed infiltration by an undifferentiated carcinoma. He was again discharged without the aid of the respirator, although he was dyspneic on slight exertion.

In July he was readmitted to the hospital because of sudden inability to swallow and breathe. In addition severe pain had developed over the right side of the chest during the preceding 2 weeks.

Physical signs were the same as on previous admissions, as were the x-ray films. Although the patient made some initial gains in response to therapy, by the 3d week after admission he was confined to the respirator. A tracheotomy was performed in the 5th hospital week to facilitate suctioning of the thick mucous secretions, which were constantly obstructing the respiratory tract. He became progressively weaker despite massive doses of prostigmine and octamethylpyrophosphoramid. On September 17, while in the respirator, he complained of inability to breathe and despite the administration of oxygen and vigorous suctioning through the tracheotomy tube, he became increasingly cyanotic and died.

Autopsy* was performed 3 hours after death. When the chest was opened, a huge tumor presented itself. The thymus could not be identified as such since the superior mediastinum was completely obliterated by the mass, which also extended down between the pericardium and right lung. The tumor consisted of large, discrete and confluent grayish-pink, cauliflower-like nodules. Yellowish, necrotic areas were present throughout, and many of the nodules showed cystic degeneration.

The tumor, which had infiltrated the right pleura and obliterated the pleural space, was firmly adherent to the chest as well as to the lung, and part of it had protruded into the 4th intercostal space at the anterior axillary line. The mass was plastered down over the anterior surfaces of the great vessels, trachea and bronchi, but no compression or invasion was noted. Several of the paratracheal lymph nodes appeared to be involved by the tumor.

The pericardial cavity was obliterated by fibrous adhesions, and several small nodules were found on the parietal surface of the pericardium but had not eroded through.

The right leaf of the diaphragm was also involved by direct extension. The tumor penetrated to the peritoneal surface of the diaphragm and compressed the upper surface of the liver.

No tumor was found in the left side of the thorax, although the left pleura was thickened. Both lungs were found to be slightly hemorrhagic; no tumor tissue was present. The heart weighed 350 gm. and appeared normal. The coronary arteries, although moderately atheromatous, were patent throughout.

The liver was somewhat enlarged, but no tumor tissue was found on section. The esophagus had 3 small superficial mucosal ulcerations just above the cardia. The rest of the gastrointestinal tract, the pancreas and the biliary system were normal, as were the kidneys and adrenal glands. The thyroid gland was of normal size and consistence. There were no gross lesions of the brain or spinal cord.

On microscopical examination the tumor consisted of sheets and nests of epithelial cells with scattered masses of lymphocytes throughout. A vascular, fibrous stroma was more marked in some places than in others, and there were numerous necrotic areas. The epithelial cells were of uniform size but showed considerable variation in chromatin content. Many mitotic figures were seen. There was only a slight tendency to perivascular rosette formation and palisading.

The myocardium was normal, but the epicardium was very fibrotic. Both lungs revealed scattered areas of hyaline thickening, thickening of the alveolar walls and considerable congestion. The pleura of the right lung was invaded by nests of tumor cells, and that of the left was markedly fibrosed but uninvolved by the neoplasm. One pretracheal lymph node contained tumor cells.

The liver was normal except for the seeding of tumor cells on the serosa. There was no parenchymal involvement. A section through the esophageal ulcerations showed loss of mucosa and marked infiltration by polymorphonuclear leukocytes.

All other abdominal organs were microscopically normal, as were the brain and spinal cord. A section of muscle was also normal.

The final pathological diagnoses were malignant thymoma, with involvement of the mediastinum, right pleura, parietal pericardium, chest wall, diaphragm and peritoneum, and radiation fibrosis of the pleura and pericardium.

*M. G. H. No. 15751. Performed by Dr. Leonard Atkins.

Pathology of the Thymus in Myasthenia Gravis

Although Symmers[21] believed that the tumors associated with myasthenia gravis could arise from any of the cellular elements of the thymus, most authors now agree that such a neoplasm is of a single type. Thus, although lymphomas, Hodgkin's granulomas and fibrosarcomas may originate in the thymus, the tumor commonly, if loosely, referred to as thymoma is the one characteristically found in these cases. The thymoma is made up of large, pale-staining epithelial cells mixed with varying proportions of lymphocytes. The epithelial cells show some tendency to form perivascular pseudorosettes and to palisade along trabeculae.[14] It is usually impossible to distinguish microscopically between benign and malignant thymomas, since in spite of the ability of the malignant form to infiltrate widely, it lacks the usual cytologic criteria for malignancy and may be identical to the benign variety in appearance.

In the case presented above, a good deal of confusion was caused by the fact that biopsy of an axillary lymph node revealed neoplastic tissue. For a time the possibility that the mediastinal mass seen by x-ray represented an independent bronchiogenic carcinoma was considered, since malignant thymomas have never been known to undergo lymphatic metastasis. The autopsy, however, demonstrated that the "metastasis" in the axilla actually was due to erosion of the chest wall by direct extension. The involvement of the peritoneum by extension through the diaphragm is very unusual.

However, this peritoneal involvement should not be interpreted as a metastasis since there was no evidence of a true embolic phenomenon. The malignant appearance of the tumor tissue, with the presence of many mitotic figures, is unusual in thymoma, and may offer some explanation for the unusual manner of its dissemination.

As noted above, about 85 per cent of thymus glands examined in cases of myasthenia are not neoplastic and, in fact, are usually of normal gross appearance. The degree of involution shown by the glands is consistent with the age of the patients as a rule, but occasionally involution is delayed.[10] These facts have been confirmed in recent experiences with the therapeutic use of thymectomy.[12, 22, 23]

Norris[7] maintained that even in the absence of abnormal enlargement, the common factor in myasthenia gravis without tumor was epithelial hyperplasia. However, this was denied by Sloan,[24] who pointed out that the amount of epithelial tissue was variable in these glands, but that the more characteristic abnormality was the presence of lymphoid germinal centers in the absence of generalized lymphadenopathy. This finding has been supported by the observations of many others.[9, 10, 12] Castleman and Norris[9] state that normal thymus glands do not contain these germinal centers, but that they appear in 75 per cent of patients with myasthenia gravis without tumor; although similar changes are found in occasional cases of Addison's disease, hyperthyroidism and acromegaly, these authors believe that they do not occur with any such striking frequency. The presence of such lymphoid centers is therefore considered to be nearly pathognomonic of myasthenia. It is interesting that in all the diseases in which these centers appear, some degree of muscle weakness may occur, though, to be sure, it is not of the same sort.

The Role of the Thymus in Myasthenia Gravis

The basic defect in myasthenia gravis is best described by an electromyographic abnormality discovered by Jolly[1] and known as the myasthenic reaction. This has been elaborated on by many workers,[25-27] who have demonstrated that the action potential of muscle in response to a single nerve stimulus is maximal in myasthenia and in normal persons. Neuronal transmission and muscular response to direct stimulation are not impaired. However, with repetitive stimulation of the nerve, the action potentials rapidly diminish in myasthenia, whereas in normal muscles they stay at the same level in accordance with the all or none law. Since both the muscle and the nerve in myasthenia behave normally, it is generally accepted that the defect that produces the myasthenic reaction must be caused by interference of transmission at the myoneural junction.

That some humoral agent is involved in the production of this neuromuscular defect seems probable. On clinical grounds, the occurrence of a transient muscular weakness that responds to prostigmine in infants born of myasthenic mothers[28-30] suggests transport of such an agent across the placenta. Furthermore, Walker,[31] some years ago, demonstrated that exercise of the muscles of the hand could increase the severity of ptosis in myasthenic patients and that this could be prevented if a pressure cuff blocked the circulation of the exercising muscles. Whether or not these muscles produced an abnormal substance capable of inhibiting transmission at the neuromuscular junction, or whether the exercising muscles produced only some normal metabolite to which the myasthenic person is peculiarly susceptible was not made clear. Other evidence in favor of a humoral factor, however, is cited below.

As repeatedly pointed out,[32, 33] the defect in myasthenia can be explained in several ways in terms of the modern chemical theory of neuromuscular transmission. In the first place there may be an excess of cholinesterase at the neuromuscular junction that removes the acetyl choline as it is produced. Secondly, there may be an actual reduction in the amount of acetyl choline produced at the nerve ending. Finally, some curariform agent may be present that in effect blocks the depolarizing action of acetyl choline on the muscle plate.

There is little evidence for the first hypothesis. It has been demonstrated that both the plasma and nerve cholinesterase activities of the blood and muscle are normal in myasthenia.[34, 35]

The second possibility was first postulated by Trethewie[36] and received considerable support from the work of Torda and Wolfe.[37-39] These workers pointed out that patients with myasthenia are extremely sensitive to intra-arterial administration of acetyl choline, and that this substance will cause involuntary contraction under these circumstances, whereas in the normal person it will actually produce weakness.[40] It was therefore believed that in myasthenia only a small amount of acetyl choline is present at the myoneural junction and that its increase results in a normal contraction, whereas any increase in the normal amount will result in blocked transmission, presumably because of the well known nicotinic effect of an excess of acetyl choline. Thus, the authors believed that there is an inability to synthesize or release a sufficient amount of acetyl choline in myasthenia. They claimed that the serum dialysate of myasthenic patients as compared with the serum of normal persons, would significantly decrease the production of acetyl choline when added to an in vitro preparation of frog brain. They also believed that the thymus is responsible for the production of this agent of anti-acetyl choline synthesis and that ether extracts

of the thymus, when injected subcutaneously into normal animals, produce this inhibitory effect on their serum.[38] The results of these experiments have, however, been challenged.[41, 42]

The final possibility, that myasthenia is produced by the presence of a circulating curariform substance, has received a good deal of support. McEachern,[32] who was among the first to champion this point of view, could find no such substance in the blood, however, urine or thymic extracts. However Harvey et al.[40] pointed out that the electromyographic and clinical effects of partial curarization are almost identical with those found in myasthenic patients. Thus, the muscles principally affected by partial curarization are the same as those affected in myasthenia (primarily bulbar, later those of the extremities and finally those of the trunk). In both, prostigmine has a salutary and quinine an aggravating effect. Wilson and Stoner,[33] some years ago, demonstrated that myasthenic serum contained a substance, soluble in alcohol, that produced a curare-like block in an isolated nerve-muscle preparation. These authors doubted if insufficient acetyl choline was produced by cholinergic nerve endings, since muscarinic functions were by and large intact in myasthenia. It is agreed[32, 40] that the thymus is the most likely source of a curariform agent, and Harvey[22] demonstrated an improvement in electromyographic abnormalities in several myasthenic patients after thymectomy.

It is naturally tempting to ascribe to the thymus a primary role in the pathogenesis of myasthenia. The literature of the early part of this century is full of reports that purported to show that the thymus had an endocrine function and that in particular it was concerned with maturation, since its development and involution parallel the growth curve. In 1919 Park and McClure[43] convincingly demonstrated that neither thymectomy nor the administration of thymic extracts appreciably altered the growth and development of young dogs. Since then, in this country at least, the thymus has been relegated to the role of an unusually well developed mass of lymphoid tissue. It is of some note, however, that the thymus is embryologically derived from the third branchial pouch, from whose entodermal tissue the thyroid and parathyroid glands are also derived. Lymphocytic invasion of this epithelium occurs only later in embryologic development.

It appears that the thymus, although it may not be primarily an endocrine organ, is at least one that is largely under the control of other hormones. The involution of the organ, which occurs with adrenocortical stimulation, is well known, and contrariwise, it is apt to be enlarged in Addison's disease. Castration also leads to enlargement of the thymus.[44] Finally, the gland is enlarged in most cases of hyperthyroidism,[45] and it has recently been recognized that thyrotoxicosis is a frequent complication of myasthenia gravis.[46, 47] Eaton,[48] in his extensive experience at the Mayo Clinic, has found that fully 6 per cent of myasthenic patients have hyperthyroidism.

It has been postulated by some German workers[49, 50] that although the thymus does not produce an endocrine secretion in the usual sense of the word, the thymocytes are charged with a hormonal substance that is released to the tissues when the cells are circulated peripherally. Bomskov[50] claimed that this thymocyte-borne hormone plays a role in glycogenolysis and that its production is under control of a specific pituitary factor, which he named "thymotropic hormone." Thymotropic hormone was said to be identical with the diabetogenic, which, according to Bomskov, was the same as the growth hormone of the pituitary gland. This hypothesis, however, has received no confirmation in this country.[51]

Although the early descriptions of the use of ACTH in the treatment of myasthenia were hopeful,[52, 53] subsequent reports have been less encouraging.[54, 55] All authors have agreed that during the administration of ACTH, muscle weakness is apt to increase, and that any improvement occurs after its withdrawal. The use of ACTH has its rationale in a number of experimental observations. Torda and Wolff[39] reported some years ago that the brains of animals treated with ACTH have an increased ability to synthesize acetyl choline. Adler[56] claimed that the muscle fatigue produced by adrenalectomy is blocked by the simultaneous removal of the thymus.

An additional observation concerning the potassium content of myasthenic muscle seems to lend further support to the use of ACTH. Cumings[57] reports that the potassium concentration in such muscle is significantly elevated. After treatment with prostigmine, potassium is discharged into the blood, with a return of muscle concentrations to normal levels. Some of this released potassium is said to enter the red cells. Since it is a well known fact that potassium is released by a contracting muscle, it might be assumed that the inability of myasthenic muscles to do so results in the piling up of that ion intracellularly. Cumings,[58] however, points out that no such increase occurs in denervated muscles and states that the increased potassium content of myasthenic muscle is a primary factor in that disease though not necessarily a cause of it. This situation might be similar to that which prevails in periodic familial paralysis.[59] It also seems that the occasional success of potassium chloride in the treatment of myasthenia may be due to the diminished intracellular-extracellular ratio of potassium. In this regard it should be noted that an increased concentration of extracellular potassium has a decurarizing action.

It is perhaps puzzling that in view of these experimental facts ACTH produces an increased

muscle weakness in myasthenia. However, it is entirely possible that the well known catabolic (or antianabolic) and muscle-wasting effects of that hormone overrule any other benefits that might result from its administration. In patients with Cushing's disease this weakness is pronounced. It may also be postulated that in cases in which improvement follows the discontinuance of ACTH, improvement in the electrolyte distribution or in acetyl choline synthesizing ability outlives the catabolic effects.

Out of the welter of facts and theories advanced in explanation of the basic derangement in myasthenia gravis, only a few things can be stated with certainty. The role of the thymus remains unclear, but whether or not it plays a primary role in the pathologic process, it seems apparent that there are humoral factors involved. There is at present no evidence that the thymus has an endocrinologic role, but the possibility remains. The thymus, however, seems to be a target organ for a variety of hormones. The possibility that there is an intracellular electrolyte disturbance also deserves fuller investigation, possibly with isotopic chemical technic.

Summary

An unusual case of exthoracic spread of a malignant thymoma associated with myasthenia gravis is reported.

The pathology of the thymus in myasthenia gravis with and without thymoma is discussed.

The possible role of the thymus in the pathogenesis of myasthenia is briefly reviewed. The exact mechanism by which this disease is produced remains unclear, but the weight of evidence indicates that a humoral factor interferes in some way with transmission of the nerve impulse across the neuromuscular junction. The possible relation of this to intracellular electrolyte abnormalities and to the therapeutic use of ACTH is discussed.

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MEDICAL INTELLIGENCE

THE BALTHAZAR-FOSTER MURMUR AND FOSTER'S RULE*

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ERRONEOUS concepts persist tenaciously in clinical medicine. One of these is the eponym, "Foster murmur," sometimes given to a particular transmission of the murmur associated with rupture of a cusp of the aortic valve. This communication traces the origin of the terms, "Balthazar-Foster murmur" and "Foster's rule," notes the interpretation given to these terms, and presents relevant clinical and pathological evidence. Because of their association with the Austin-Flint murmur, that anomaly is also mentioned.

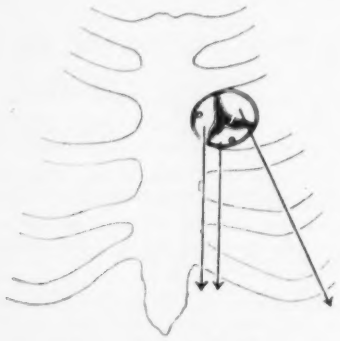

FIGURE 1. *Foster's Rule.*
The direction of transmission of the aortic diastolic murmur arising from the rupture of a particular cusp of the aortic valve is indicated by the arrows.

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FOSTER'S DESCRIPTION

While professor of clinical medicine at Queen's College in Birmingham, Foster,[1, 2] in 1866 and 1867, reported a case of injury to the aortic valve in a thirty-three-year-old man. Post-mortem examination demonstrated "a tearing of the left semilunar segment of the aortic valve." Foster indicated that the ruptured cusp had no coronary-artery ostium in its adjacent sinus of Valsalva. The patient had a loud murmur of aortic regurgitation, a mitral systolic murmur well transmitted to the axilla and also, at the apex, " a peculiar prolongation of the second sound sometimes *almost* a murmur. . .no doubt due to the propagation of the murmur produced by regurgitation through the injured valve."

In 1873 Foster[3,4] reported 2 further cases of rupture of the aortic-valve cusps in thirty-three-year-old men. In each a cusp, from which a coronary artery in its adjacent sinus of Valsalva arose, was ruptured. In each the diastolic murmur of aortic insufficiency was transmitted well to the ensiform cartilage, but not to the heart's apex.

In a lecture on rupture of the aortic valve Foster[4] stated his rule (Fig. 1) that "incompetency of the left leaflet is associated with transmission of the diastolic murmur to the apex and that insufficiency of either the posterior or right leaflets results in transmission of the murmur to the ensiform." He considered the transmission of the murmur to be of prognostic significance. In his book on clinical medicine[5] published in 1874 he devoted a chapter to rupture of the aortic valves. Without warning he changed his nomenclature of the aortic valves, referred to the noncoronary leaflet as a posterior segment and changed his rule accordingly.

INTERPRETATIONS OF THE FOSTER MURMUR

Guitéras[6] believed that Foster was describing an Austin-Flint murmur. Cole and Cecil[7] quoted Foster's observations and stated that he had confirmed them in several cases. Herrmann[8] believed that Foster was describing the transmission of the aortic diastolic murmur to the apex, as noted by Cole and Cecil in aortic regurgitation. This transmission he termed a "Foster murmur," and at-

tached prognostic importance to it and to the Flint murmur.[9] Gouley[10] called the Foster murmur "an axillary murmur in aortic insufficiency."

Evidence Regarding Foster's Rule

In Herrmann's[8,11] animal studies injury to one of the coronary cusps of the aortic valve resulted in transmission of the murmur to the heart's apex. Injury to the posterior (noncoronary) leaflet usually resulted in the Flint phenomenon. Herrmann[8] cited 2 cases of the Flint murmur in patients with syphilitic aortic regurgitation; the findings at autopsy agreed with his experimental study. In 4 of 17 cases of aortic regurgitation studied by Cole and Cecil, both an Austin-Flint murmur and the transmitted aortic diastolic murmur were heard at the apex. White[12] and Gouley[10] also noted this. The studies of Gouley, in contrast to those of Herrmann, indicated that the Flint murmur occurred when regurgitation involved predominantly the right (coronary) cusp at its junction with the posterior (noncoronary) cusp. Nichols[13] believed that transmission of the murmur to the right toward the liver meant that only the posterior cusp was involved. Studies of paraffin models in syphilitic aortic regurgitation by Scott[14,15] indicated, regardless of which cusp was most diseased, that the regurgitant

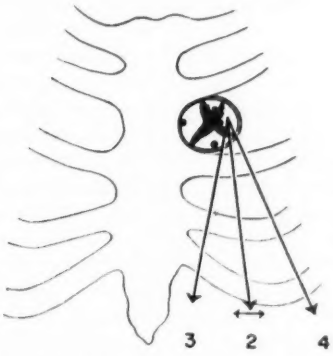

Figure 2. *Direction of Transmission of the Diastolic Murmur in 9 Observed Cases of Incompetence of the Noncoronary Cusp of the Aortic Valve.*

stream was predominantly through the center of the valve aperture.

Cases of aortic regurgitation are not ideal for proof of Foster's rule. Few suitable cases in which one aortic leaflet was injured and in which the murmur was described soon after injury are recorded. Bramwell[16] observed a patient with rupture of the left coronary segment of the aortic valve. The diastolic murmur was heard along the sternal border to the ensiform cartilage and only "slightly" at the apex. Misinterpreting Foster's nomenclature, Bramwell commented in a footnote "[this] seems to completely disprove Dr. B. Foster's theory." Porter and Williams[17] observed a patient with erosion of the right coronary segment in whom the diastolic murmur was transmitted along the sternum. With erosion of the right coronary cusp Bain and Wray[18] reported transmission of the aortic diastolic murmur to the apex. Although eversion involved the right leaflet in 2 cases and the posterior (noncoronary) in 1, Nichols[13] stated that the clinical picture was the same in each.

Personal Observations

From the Charity Hospital and Walter Reed Hospital 14 suitable records were found. Five patients were observed personally.

When the noncoronary cusp was involved the transmission of the murmur was as follows (Fig. 2): to the apex, 4 cases; to the ensiform, 3 cases; and to both areas, 2 cases. When the left coronary-artery segment was involved the following transmission was noted (Fig. 3): to the apex, 2 cases; and to the ensiform, 3 cases. An Austin-Flint murmur was present with involvement of a noncoronary cusp in 3 cases and in association with a coronary cusp in 2. The duration of life after onset of these murmurs was unrelated to the transmission of the murmur or to the occurrence of the Flint murmur.

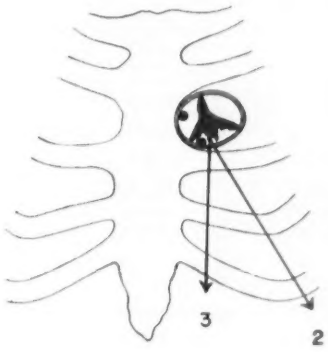

Figure 3. *Direction of Transmission of the Diastolic Murmur Observed in 5 Cases of Incompetence of the Left Coronary Cusp of the Aortic Valve.*

Summary and Conclusions

The historical origin of "Foster's murmur" and "Foster's rule" is noted. Ambiguously described, the murmur has been variously interpreted. The rule is confirmed neither by the meager evidence found in the medical literature nor by an analysis of further cases. The prediction of which cusp of the aortic valve is incompetent, either on the basis of

transmission of the aortic diastolic murmur or on the basis of a Flint murmur, is hazardous.

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NOBEL PRIZE WINNERS OF SWITZERLAND IN PHYSIOLOGY AND MEDICINE

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During a three-year sojourn in Switzerland, long famous for its watches, cheese and scenic beauty, I have been more than impressed by this little country's amazing facilities for the teaching of medicine and by the quality of medical care given.

In this respect it may be worth while briefly to review Switzerland's Nobel Prize Laureates in Physiology and Medicine. Since it is generally acknowledged that the Nobel Prize is the highest award that can be conferred on a scientist, the list of Swiss laureates should give a fairly accurate idea of the country's contribution to medical research. The following list is compiled from information published by the Nobel Prize Committee in Stockholm, and the description of each contribution is based on the citation at the time of the award:

1909 -- Theodore Kocher, professor of surgery at the University of Berne, 1841-1917, awarded the Nobel Prize "for his work on the physiology, pathology, and surgery of the thyroid gland." (He is known to every doctor for his maneuver.)

1937 -- Paul Karrer, professor of chemistry at the University of Zurich, awarded the Nobel Prize "for his investigation of carotenoids and flavins, and for his research on vitamins A and B_2."

1948 -- Paul Herman Muller, research worker in the scientific laboratories of the firm of Geigy and Company, of Basel, awarded the Nobel Prize "for his discovery of the strong effect of DDT as a contact poison against a number of arthropods."

1949 -- Walter Rudolph Hess, professor of physiology and head of the Department of Physiology at the University of Zurich, awarded the Nobel Prize "for his discovery of the functional organization of the diencephalon for co-ordination of the activity of internal organs."

1950 -- Thaddeus Reichstein, professor of organic chemistry at the University of Basel, "for discoveries regarding the hormones of the adrenal cortex, their structure and biologic effects." (Prize shared with Kendall and Hench, of the Mayo Clinic.)

Since Switzerland has produced Nobel Prize laureates in recent years it is apparent that Swiss research in physiology and medicine is not living on past glory but is going strong in the present. With one prize winner in each of the three years, 1948, 1949 and 1950, Switzerland stands alone with the United States as one of the only two countries in the world having placed winners three years straight. This performance is all the more amazing when one considers that the entire population of Switzerland is approximately equal to that of Chicago (4,600,000).

Other countries that have placed winners many times for the Nobel Prize in physiology and medicine are the United States, 10 times (population, 160,000,000); Germany, 8 times (population, 67,000,000); Great Britain, 7 times (population, 50,000,000); France, 4 times (population, 41,000,000); and Denmark, 4 times (population, 4,200,000).

When the prize has been awarded to two or more members of the same country, divided for the same work, it has been counted as one award (as in the award to Fleming, Chain and Florey, who received the prize together for their work on penicillin).

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

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CASE 39251

PRESENTATION OF CASE

A fifty-nine-year-old furniture-shop worker was admitted to the hospital because of fever of unknown origin.

The patient had been in good health until two and a half weeks before entry, when malaise, fever, shaking chills, nausea and vomiting occurred. Four persons who worked in the same furniture shop also developed similar symptoms at about that time, but they subsequently recovered. The patient stayed in bed for three days and took liberal amounts of aspirin, without alleviation of symptoms. The symptoms persisted up to the time of admission with shaking chills lasting ten or fifteen minutes each day, drenching perspiration and marked anorexia. The temperature ranged from 101 to 105°F. He had been confined to bed for two weeks before admission. For one week before admission persistent hiccoughs, lasting four or five hours at a time, occurred every day. For four days before admission he had taken 750 mg. of terramycin, without improvement. There had been no cough, expectoration, dyspnea, chest pain, hemoptysis, headache or conjunctivitis. He denied having a sore throat, nose bleeds, arthralgia, myalgia, skin lesions, abdominal pain, diarrhea, constipation or jaundice. There was no history of direct contact with animals, including birds. There was no known exposure to unusual chemicals. He denied ingestion of unpasteurized milk.

He had taken several ounces of whiskey daily for ten to fifteen years; however, his dietary intake was said to have been adequate. Diabetes mellitus had been diagnosed twelve years previously, and he had been maintained on 12 units of protamine zinc insulin daily. Urine sugar tests, which were infrequently done, were reportedly blue to green.

Physical examination showed a warm, flushed, stuporous and dehydrated man. There were decreased breath sounds and crepitations at the left lung base posterolaterally, as well as a few crepitations at the right lung base. The cardiac apex was at the left midclavicular line; the rhythm was regular, and there was a Grade 2 systolic murmur at the apex but no other murmurs. The abdomen was soft, and the liver edge, which was not tender, was palpable 2 fingerbreadths below the right costal margin in the midclavicular line. The spleen was not felt.

The temperature was 103°F., the pulse 120, and the respirations 34. The blood pressure was 120 systolic, 60 diastolic.

The urine had a specific gravity of 1.018 and gave a + test for albumin and an olive-green test for sugar. The sediment contained 2 red cells, 3 white cells and a rare hyaline cast per high-power field. Examination of the blood revealed a hemoglobin of 15 gm. per 100 cc. and a white-cell count of 7300, with 77 per cent neutrophils, 16 per cent lymphocytes, 4 per cent monocytes, 1 per cent eosinophils and 2 per cent basophils; the majority of the neutrophils contained toxic granules. The fasting blood sugar was 118 mg., the nonprotein nitrogen 18 mg., the total protein 5.1 gm., the albumin 2.7 gm., the globulin 2.4 gm., the serum bilirubin 0.9 mg. total, and the alkaline phosphatase 3.0 units per 100 cc.; the sodium was 133 milliequiv., the chloride 88 milliequiv., and the carbon dioxide 27.5 milliequiv. per liter. The cephalin flocculation was ++ in twenty-four and forty-eight hours. Typhoid, paratyphoid and Brucella agglutinations were negative. A stool was guaiac negative; no amebas were demonstrated. Stool culture grew out a pure culture of hemolytic *Staphylococcus aureus*. Throat culture grew out abundant alpha-hemolytic streptococci and a few *Staph. albus*. Urine culture and aerobic and anaerobic blood cultures showed no growth. A chest film taken with a portable machine demonstrated a high diaphragm, especially on the right, but no obvious localized pulmonary disease. An electrocardiogram disclosed a sinus tachycardia and arrhythmia, with a rate varying between 100 and 110, a PR interval of 0.12 second and a tendency to right-axis deviation; the T waves were low and upright in Leads 1 and 2, flat in Leads 3, aVL and aVF, with a rather low voltage of all complexes, low and upright in Lead V_1 and upright in Leads V_2, V_3, V_4, V_5 and V_6.

The patient was digitalized and given large dosages of various antibiotics including penicillin, streptomycin, erythromycin and chloramphenicol, as well as sulfadiazine. During the first ten days in the hospital he had diarrhea with as many as fourteen stools daily. On the tenth hospital day *Staph. aureus* was no longer found in the stool, which grew out abundant *Escherichia coli* on culture; it was negative for enteric pathogens. A roent-

genogram of the chest on the fifth hospital day demonstrated a hazy mottled density and reduction in size of the posterior basal portion of the left lower lobe (Fig. 1). There was a lesser degree of mottled and linear density below the right hilus. The left ventricle appeared rather prominent. An electrocardiogram on the twelfth hospital day showed an increase in rate and inverted T waves in Leads 1, 2, aVL, V_2, V_4, V_5 and V_6. The apex of the heart extended to the anterior axillary line, and the pulse was irregular. X-ray films of the chest on the eighteenth hospital day disclosed that the diaphragm had risen and that there was more atelectasis with associated consolidation in the lower lung fields, most marked on the right. The heart shadow had not changed materially. Urine culture on the twenty-eighth hospital day grew out a moderate number of oval-bodied yeasts. Pulmonary rales at the bases, especially on the left, were noted throughout the course of the illness. During the entire hospitalization the patient was confused and appeared critically ill. He was never afebrile, having a temperature ranging from 100 to 105°F. The pulse rate ranged between 120 and 150. Numerous white-cell counts varied between 4200 and 6400, with the exception of one count of 2000. Leukopenia did not persist, however, and the count returned to the usual levels after chloramphenicol was discontinued. The white-cell differential count on admission was typical of many others made subsequently. The diabetes was treated with regular and protamine zinc insulin, but blood sugar levels as high as 314 mg. per 100 cc. were noted and urine specimens almost always gave an orange to yellow sugar test. The urine had a specific gravity ranging from 1.020 to 1.036 and most often gave a ++ test for albumin; the sediment contained few to many red cells, relatively few white cells and varying numbers of granular or hyaline casts per high-power field. The nonprotein nitrogen never rose above normal levels. Repeated agglutination studies were consistently negative. The blood hemoglobin was usually low normal although numerous blood transfusions were given. The sodium ranged as high as 155 milliequiv., the chloride 111 milliequiv., the potassium 5.4 milliequiv., and the carbon dioxide, which was usually elevated, 32 to 34 milliequiv. per liter.

Terminally, the patient was stuporous, the lungs were full of rales, and the abdomen was distended. The temperature rose to 107°F., and he died on the thirty-fourth hospital day.

Differential Diagnosis

Dr. Reed Harwood*: I might start by trying to wring a few clues from the radiologist.

Dr. Stanley M. Wyman: In the first x-ray examination of the chest, which was made with a portable machine, no obvious intrinsic disease is seen. There may be some patchy density in the central lung field, but I think this is probably atelectasis. The next film made five days later in the department is of better quality and shows some patchy atelectasis, with perhaps some consolidation in the left lower lobe (Fig. 1). There is also some atelectasis in the right lower lobe. The upper lung fields do not seem grossly abnormal. The heart shadow is not remarkable. The lateral film taken

Figure 1.

on the same day demonstrates the atelectasis lying in the posterior portion of the left lower lobe to better advantage. Ten days later the diaphragm has risen bilaterally, and there is less evidence of pneumonitis. What one sees is apparently chiefly atelectasis in the lower lung fields. On none of these examinations were we able to see any localized process elsewhere in the lungs.

Dr. Harwood: From the description I had expected to see more in the films. The outstanding feature in this case, it seems to me, was acute sepsis, and the peculiar feature of the case is that the nature and the locus of the infection were obscure. I might first ask, Was the patient's illness related to that of the other 4 who worked in the same shop? I do not think so. My guess is that there was an epidemic of grippe that coincided with the onset of the patient's illness, but I shall concede that an identical infection in 5 persons could have led to death in 1 because of his lowered resistance, or could have been followed by a fatal secondary complication.

The bacterial data were particularly puzzling. The patient was acutely ill for two and a half weeks, and yet he had no definite localizing symptom. On admission he had a severe diarrhea; the

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stools yielded a pure culture of *Staph. aureus*. It seems unlikely that the symptoms of enteritis would have been masked for two and a half weeks if that had been the source of his infection; hence this development must have been a new complication or possibly the result of antibiotic treatment. It is amazing to me that pathogenic bacteria were cultured from no other source during a septic illness that lasted for fifty days. The only explanation that I can offer is that one or more of the antibiotics used suppressed growth of bacteria in the blood, urine and throat, without overcoming infection in whatever organ or organs were involved. The use of antibiotics before adequate bacteriologic information is obtained is perhaps justified in an acutely ill patient such as this one, but it is appropriate to point out here the obvious danger of treatment first and then speculating about the diagnosis, a practice that is all too common in this day of rapid and miraculous cures. Let us turn now to a consideration of this patient's cardiac status.

During the thirty-four days in the hospital there was evidence of increasing heart size. Dr. Wyman, do you think the heart became enlarged?

Dr. Wyman: I cannot be sure of any real increase in the size of the heart. I think the apparent increase is due to the higher position of the diaphragm, the heart then lying more transversely.

Dr. Warren Point: The heart did enlarge markedly after the x-ray films were taken.

Dr. Harwood: The reported increasing size of the heart and increasing congestion of the lungs do not help me much with the primary diagnosis. My interpretation of this is that cardiac dilatation developed as the result of a severe illness with probable antecedent coronary-artery disease, which we might expect in a patient of this age with long-standing diabetes. The findings in the lungs were no doubt partly due to congestive heart failure; however, atelectasis and bronchopneumonia are also likely to have been present. Bacterial endocarditis should be considered, but the absence of embolic phenomena, of changing heart murmurs and of positive blood cultures makes that diagnosis seem extremely unlikely. Dr. Castleman kindly let me look at the electrocardiogram; I am not too impressed with the evidence of myocardial infarction in this case. I was going to include that in my diagnosis, but I am less sure of it after seeing the electrocardiogram.

The patient had had diabetes for at least twelve years; this fact suggests that the diagnosis of pyelonephritis of the necrotizing papillitis type should be considered. A brief review of the literature indicates that it is an uncommon disease, seen only occasionally in nondiabetic persons with urinary-tract obstruction and more commonly in diabetic patients with or without obstruction. It is an acute, often fulminating, febrile disease and is usually fatal. The diagnosis is usually suggested by obvious urinary symptoms and laboratory findings, including nitrogen retention. Cases are on record, however, in which localizing symptoms are lacking, urinary findings are minimal and renal failure is not evident. In diabetes the disease is usually bilateral, but occasionally it has been confined to one kidney. At autopsy there is necrosis and sloughing of the renal papillae associated with various degrees of infection of tubules, pelves, ureters and bladder. Other common findings are single or multiple kidney abscesses, cortical abscesses, perinephric abscesses and thrombophlebitis of the renal veins. *Esch. coli* and *Staph. aureus* are the most common infectious agents. Usually, intercapillary glomerulosclerosis is associated with it; arteriosclerosis, myocardial infarction and bronchopneumonia are common complications.

I realize that there are numerous objections to the diagnosis of necrotizing papillitis. Yet the clinical course was sufficiently similar to that of some cases reported in the literature to make the diagnosis attractive, particularly since no good clues point in any other direction. My diagnoses, therefore, are necrotizing papillitis, perhaps with abscess in and around the kidneys, bronchopneumonia and congestive heart failure; because the nonprotein nitrogen was persistently normal I shall postulate that the disease was largely confined to one kidney.

Whether the diagnosis is correct or not, I want to take this occasion to point out the frequently serious consequences of mild urinary-tract infection in diabetes. One of the important reasons for continued periodic follow-up study of diabetic patients is to provide early diagnosis and prompt, vigorous treatment of asymptomatic urinary-tract infection, which is frequent in diabetes. Pyuria in a diabetic patient should never be ignored. Catheterization should be avoided whenever possible or performed only under the most rigidly aseptic technic. In cases of obscure fever in diabetic persons the urinary tract should be thoroughly studied.

Dr. Daniel S. Ellis: This patient had an indwelling catheter in the bladder throughout most of his illnesses. Would you not expect him to have had more urinary-tract findings or more findings in the urinary sediment if he had pyelonephritis?

Dr. Harwood: I should, but, as I said, a few patients have been reported to have died with this disease who have had minimal findings in the urinary sediment.

A Physician: Would Dr. Harwood comment on the oval-bodied yeast found in the urine culture?

Dr. Harwood: I doubt if he had a yeast infection as the cause of death. Of course, many infections should be included in the differential diagnosis. The yeast was a late finding and might have been the result of the indwelling catheter or of the large amount of antibiotics.

Dr. Farahe Maloof: This patient was diabetic, had a persistent, high fever in spite of chemotherapy, and had negative urinary cultures; would you consider miliary tuberculosis?

Dr. Harwood: That is a possibility. Let's ask Dr. Wyman if holding in mind that the patient had been acutely ill for fifty-four days he thinks the x-ray films of the chest are consistent with that diagnosis. I think the sudden onset of shaking chills fifty days before death is against miliary tuberculosis.

Dr. Wyman: That we do not see miliary lesions in the lung does not argue against the diagnosis. A number of patients who have shown miliary tuberculosis at autopsy have had no demonstrable lesions in good chest films. These films are less than ideal because the patient was extremely ill.

Dr. Harwood: I should like to make it clear that I avoided a painstaking listing of all the possible diagnoses. I took a long shot.

Dr. Point: This patient had two different illnesses. One was related to the illness the other men in his shop had, which improved after a few days. He was ambulatory for a week at home and thinking of going back to the office when he became sick and had chills again.

Dr. Lamar Soutter: Did you think he had liver disease, Dr. Harwood?

Dr. Harwood: I do not think he had much liver disease.

Dr. Ellis: I came in on this case after the patient had been sick for a month. I thought he had a large liver, and he had a positive flocculation test. The first time I saw him I thought he did have liver disease and was in impending liver failure.

Dr. Harwood: Did you find any telangiectasis?

Dr. Ellis: He had no spiders and no jaundice; he had a large, palpable liver, and the flapping tremors that we see in hepatic coma. I realized that that was not the whole picture and thought we were dealing with infection. The antibiotics were given to him in an attempt to control the staphylococcal enteritis, which worried everybody. We thought the antibiotics had knocked the normal organisms out of the gastrointestinal tract and that *Staph. aureus* had taken over. The patient was seen by the various specialists in infectious disease, who suggested some of the antibiotics used, none of which proved to be of much avail. I thought that he had primary infection and a previously cirrhotic liver that was reacting poorly under stress of the infection, whatever that was. As time went on we were less sure of the diagnosis; everybody thought he had infection. When he died I do not think any of his physicians were sure of the diagnosis.

Clinical Diagnoses

Acute infection, cause unknown, ?miliary tuberculosis.
?Pneumonitis.
Liver failure.
Diabetes mellitus.

Dr. Reed Harwood's Diagnoses

Pyelonephritis, with necrotizing papillitis.
Bronchopneumonia.
Congestive heart failure.
Diabetes.

Anatomical Diagnoses

Miliary tuberculosis.
Hemochromatosis.
(Diabetes mellitus.)

Pathological Discussion

Dr. Benjamin Castleman: At autopsy there was a great deal in the lungs; in the right upper lobe there were half a dozen whitish, granular areas measuring up to 1.5 cm. in diameter that on gross examination looked like caseous tubercles. We found a few smaller lesions, about 0.5 cm. in diameter, in the left upper lobe. Scattered throughout both lower lobes were what were interpreted on gross examination as miliary tubercles. The liver was enlarged, was a brownish orange and contained a few lesions that look suspiciously like tubercles on gross inspection.

Microscopically, the caseous lesions in the upper lobes were tuberculous; apparently, the infection had broken into the blood stream and had produced a miliary spread because we found tubercles in almost every organ in the body—in the liver, the spleen and especially the bone marrow. They were so numerous in the bone marrow that it is quite possible that an aspiration or biopsy of the bone marrow would have revealed tubercles.

In the liver, in addition to the tuberculosis, there was well marked cirrhosis of the pigment variety—that is, hemosiderin granules. Hemochromatosis usually results in hemosiderin deposits in and fibrosis of the pancreas and affects the islands of Langerhans, producing diabetes. In this case there was marked hyalinization and obliteration of most of the islet tissue, often seen in the usual nonhemochromatosis case of long-standing diabetes. Only an occasional islet contained hemosiderin, but there was not much fibrosis in these areas. I believe this patient had the usual form of diabetes mellitus associated with hyalinization of the islets rather than with the hemochromatosis, although it is conceivable that the hemochromatosis aggravated the underlying diabetes.

Dr. Point did make the correct diagnosis of tuberculosis before the patient died. Would you like to comment?

Dr. Point: The patient had congestive heart failure about two weeks after entry, and he had to have

diuretics to survive. He went into cardiac collapse at one time. My opinion was that he had liver disease; in fact, the admitting diagnosis was abscess of the liver. He was an alcoholic, had fever and on arrival had an enlarged liver. The liver shrank to a normal size in two weeks, but the flapping tremor persisted throughout most of the hospitalization; surely, if he had had severe liver disease he would have died of hepatic coma long before he did. He was known to have been a much heavier alcoholic than he would admit. The diabetes went back twelve years, and the alcoholism about two or three years. The patient improved in the first eight days in the hospital so the streptomycin was stopped because it was thought that vestibular toxicity might develop. No one thought he had tuberculosis at that time, and therefore streptomycin was stopped and chloramphenicol and aureomycin given. With the withdrawal of streptomycin he became sicker again. The fact that he had improved on streptomycin and relapsed when the drug was withdrawn led me to suspect tuberculosis. The positive cultures for *Staph. aureus* were associated with the diarrhea, and we thought terramycin had suppressed the normal flora. A bone-marrow aspiration was planned on the day he died.

Dr. Lawrence J. Kunz: Apparently staphylococcal enteritis followed the four days' treatment with terramycin. The intestinal flora was definitely upset in that we found a pure culture of *Staph. aureus* in the stool on entry; the normal intestinal flora returned after about ten days. Cultures taken at autopsy were not abnormal except for the finding of monilia wherever we looked for it. There were at least two different species of monilia that we identified. It might be noted that during the last few days before death numerous monilia were found in the urine.

A Physician: Was anything found in the choroids of the eye?

Dr. Castleman: I do not believe that they were examined anatomically.

CASE 39252

Presentation of Case

A forty-year-old woman was admitted to the hospital because of intermittent fever.

The patient had been well until three years before entry, when she began to have bouts of intermittent fever occurring about once every four months and lasting about a week to a month. The temperature rose to 100 to 103°F. late in the afternoons. The fever was preceded by a slight chilly sensation, and accompanied by a "flushed" feeling and a "beating ache" in the joints and back. She also believed that during such episodes her stomach "swelled slightly," as though "it had a cold in it," and she had had mild anorexia but no nausea or vomiting. Fever was also accompanied by a feeling of weakness but no other symptoms. During the past several years she had lost about 23 pounds in weight. Eight months before admission she visited a clinic, because of symptoms, and was found to have an elevated sedimentation rate and negative liver-function tests and agglutinations for brucella, typhoid and paratyphoid. One month later she returned to the clinic, where she was found to have a temperature of 100°F., a normal sedimentation rate and a blood hemoglobin of 11.4 gm. per 100 cc.

She denied having drunk raw milk or having been exposed to rodents or tuberculosis. She did not have night sweats or a cough.

Physical examination showed a well developed and well nourished woman, who was slightly pale but in no distress. The heart and lungs were normal. In the abdomen, the spleen was palpable 2 cm. below the costal margin, and was firm and nontender. The liver edge was not palpable. There was no lymphadenopathy.

The temperature was 99°F., the pulse 88, and the respirations 20. The blood pressure was normal.

The urine had a specific gravity of 1.024 and was normal. Examination of the blood revealed a hemoglobin of 12.2 gm. per 100 cc. and a white-cell count of 7000, with 71 per cent neutrophils, 22 per cent lymphocytes, 6 per cent monocytes and 1 per cent eosinophils. On smear, there was slight variation in size and shape of the red cells, many appearing smaller than normal. A sedimentation rate was 12 mm. in sixty minutes.

A roentgenogram of the chest was normal. On a gastrointestinal series the esophagus was not remarkable. In the stomach, there was marked increase in the prominence of the mucosal folds, most pronounced in the proximal three fourths. These folds appeared somewhat irregular in caliber, especially in the lower proximal portions of the stomach; however, the organ seemed moderately pliable (Fig. 1 and 2). There was no significant retention of secretion. The duodenal bulb and loops were normal. The spleen appeared to be enlarged.

On the seventh hospital day an operation was performed.

Differential Diagnosis

Dr. Farahe Maloof*: This forty-year-old woman had intermittent fever for three years, slight anemia, weight loss, splenomegaly and some gastrointestinal abnormality. Since the diagnosis hinges somewhat on the x-ray findings, I will ask Dr. Wyman to describe them.

Dr. Stanley M. Wyman: The chest films, as reported in the protocol, are not remarkable. The lung fields are clear, and the heart shadow is within normal limits. The spleen as seen on these films

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from the gastrointestinal series on two separate occasions was very definitely enlarged, certainly down to this point (Fig. 1). The gastric rugae are greatly increased in size, most pronouncedly in the proximal three fourths of the stomach. On the spot film the process seems to end just below the angle of the stomach, the folds beyond that point being relatively normal (Fig. 2). Fluoroscopically, there was a very definite suggestion that the stomach could be deformed and that there was some pliability maintained in the stomach.

DR. MALOOF: Was anything mentioned about peristalsis?

DR. WYMAN: Peristalsis, if present, was certainly minimal; I do not remember seeing it.

DR. MALOOF: Were there any ulcerations?

DR. WYMAN: No; if there are any present, they are very fine serrations. I cannot be sure of any.

DR. MALOOF: Do the bones look all right?

DR. WYMAN: The bones look quite normal.

DR. MALOOF: Apparently, one of the chief symptoms was intermittent fever. There are numerous

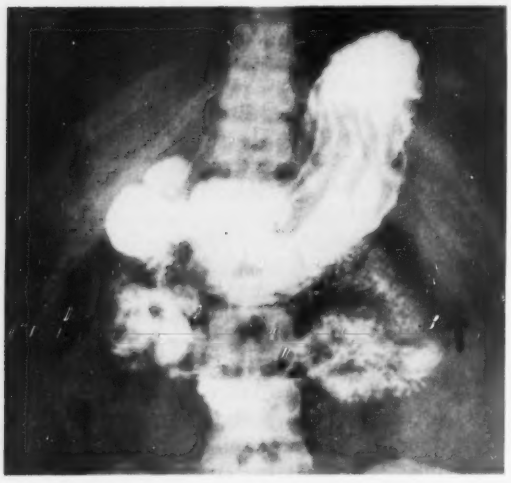

FIGURE 1. *Roentgenogram of the Abdomen. Arrow points to the lower edge of the spleen.*

diagnoses that one may entertain when discussing the cause of fever of unknown origin, but many of them are fairly well ruled out in this protocol. An article written over twenty years ago[1] describes 57 cases of fever of unknown origin that were carefully followed at the Peter Bent Brigham Hospital; no diagnosis was established in 36 cases; the diagnoses in the other 21 were tuberculosis, rheumatic heart disease, subacute bacterial endocarditis or neoplasm. On the basis of the history and findings I can eliminate rheumatic heart disease and subacute bacterial endocarditis in the case under discussion. There is little in the protocol upon which to incriminate tuberculosis. I think that neoplasm may be the diagnosis here. Other diagnoses that should be mentioned are sarcoid, berylliosis and malaria, especially if this patient had lived in the proper area. There is little to support these diag-

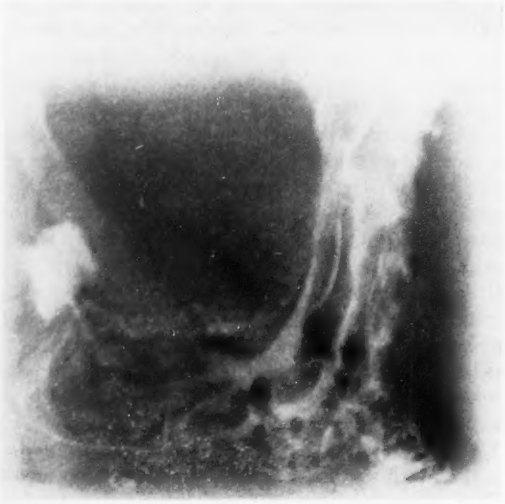

FIGURE 2.

noses. I wonder if Dr. Castleman can tell me if this patient was an Italian.

DR. BENJAMIN CASTLEMAN: She was born in New England and has lived here all her life; she is of Italian extraction.

DR. MALOOF: Dr. Bernard M. Jacobson says that he can palpate an enlarged spleen in some of his otherwise normal Italian patients; I wondered whether that was part of the picture. In addition to the fever, there were joint symptoms, which make me think of leukemia, polyarteritis nodosa, lupus erythematosus and rheumatoid arthritis; however, there is not much evidence for any of these. It might be well to know whether the joints were swollen and red or whether there was just a vague arthralgia. I do not know the significance of the swelling of the stomach. The anorexia, nausea and weight loss might go with any systemic disease. Eight months before admission she visited a clinic and was found to have an elevated sedimentation rate. I think that this is pertinent although somewhat nonspecific information. I remember 3 recent cases in which at one time the only abnormal finding was an elevated sedimentation rate; 2 of these patients were called neurotic. In the final analysis 2 had lymphoma and 1, whose case was discussed

here recently by Dr. John B. Stanbury, had carcinoma of the pancreas.[2] A month later, when she returned to the clinic, she had a temperature of 100°F., a normal sedimentation rate and a hemoglobin of 11.4 gm. She had not ingested raw milk, nor had she been exposed to rodents. I can think of no disease that is transmitted by rodents that would give this picture.

On admission the temperature, pulse, respirations and blood pressure were normal. The urine was fairly normal, which makes it difficult for me to say that the genitourinary tract—a renal infection or even a hypernephroma—was the cause of the unexplained fever. The blood count does not help. The smear is consistent with a slight microcytic anemia or with the picture noted in people of Mediterranean extraction. The normal sedimentation rate bothers me. Syphilis always has to be considered, but I do not see any mention of a blood Hinton test; I suppose it was negative.

Dr. Castleman: Yes, it was.

Dr. Maloof: I believe that this patient had lymphoma. The lack of peripheral adenopathy is not inconsistent with such a diagnosis, for in lymphoma of the gastrointestinal tract, peripheral lymphadenopathy is unusual. In contrast, patients with mediastinal lymphoma almost always have peripheral lymphadenopathy.

In the gastrointestinal tract, there was apparently a definite abnormality noted in the x-ray films. Since I thought the diagnosis was lymphoma and since I had seen only 1 case of lymphoma of the stomach, I reviewed 14 cases from the x-ray teaching file. It is interesting that in most of these the prominent folds that Dr. Wyman pointed out in this patient were present; however, 11 of the 14 also had ulcerations. One radiologist[3] states that when fairly diffuse involvement of the stomach is seen and is due to lymphoma, peristalsis is usually present although diminished, whereas if carcinoma is responsible, the presence of peristalsis would be unusual. Dr. Wyman said he did not see any peristalsis. The gastric analysis probably would not help; in the Lahey Clinic series[4] 10 out of 18 patients with lymphoma of the stomach had free hydrochloric acid. A gastric analysis and cytologic examination of the gastric contents are not mentioned, but that would not help if this was lymphoma. Mrs. Ruth Graham, of the Cytology Laboratory, has examined the gastric contents of 13 patients with lymphoma of the stomach—all were negative for tumor cells.

This might have been sarcoid. Sarcoid rarely involves the gastrointestinal tract. However, lymphoma of the gastrointestinal tract is not common either, especially if it only involves the stomach. In the series of Jackson and Parker[5] 5 per cent of over 200 patients had involvement of the gastrointestinal tract by lymphoma—3 in the stomach, 2 in the cecum, 2 in the sigmoid, 1 in the duodenum, and 1 in the esophagus. I do not know what tuberculosis of the stomach would look like.

About the operation in this patient, since the liver was not enlarged, I doubt if an aspiration biopsy was done. A splenic aspiration may have been done; however, I suppose the operation was an exploration with gastric surgery in mind. One interesting point is that the liver and spleen may look quite normal at operation and yet may be infiltrated with tumor; therefore, when the surgeon explores he should biopsy these organs.

Now I should like to ask Dr. Wyman if he thinks the x-ray findings are consistent with lymphoma of the stomach?

Dr. Wyman: They are quite consistent with lymphoma; in fact that was my diagnosis. The large folds, especially since they vary in caliber, make me think of lymphoma. A superficial, spreading type of carcinoma can do the same thing, but it is less common. The other major consideration is giant gastritis but that usually results in a more uniform caliber of the folds than occurred in this case.

Dr. Maloof: Would absence of peristalsis occur with giant gastritis?

Dr. Wyman: I think that is an unreliable observation and a difficult one to be sure about. We have been able to deform the stomach with lymphoma, with superficial carcinoma and certainly with gastritis. The reverse can be true of all three.

Dr. Castleman: Do you see a soft-tissue mass? The radiologist who took films before this patient came into the hospital reported a soft-tissue mass in the region of the cardia.

Dr. Wyman: I think that is part and parcel of the large mucosal folds. I think that was a large ruga; I cannot see any separate additional mass. Perhaps blood clot was present at one time; I do not know.

Clinical Diagnosis

Lymphoma of stomach.

Dr. Farahe Maloof's Diagnosis

Lymphoma of stomach.

Anatomical Diagnosis

Malignant lymphoma of stomach, lymphoblastic type.

Pathological Discussion

Dr. Castleman: This patient had been followed by Dr. Earle M. Chapman and was explored by Dr. Richard Sweet, who, I think, made a preoperative diagnosis of lymphoma of the stomach. That was also the diagnosis made by the radiologist from the other clinic.

At operation the stomach was about 2.5 to 3 cm. thick owing to extensive involvement of the submucosa and muscularis with malignant lymphoma, but there were no ulcerations. There were also large masses outside the stomach in the region of the upper portion, and some of them extended to the surface of the pancreas. The surgeon thought the tumor had extended into the pancreas, but on section it was not involved; I believe there was enough pressure on the splenic vein by these masses, however, to have caused the enlarged spleen. The spleen showed only congestive splenomegaly, without evidence of lymphoma. The lymphoma, I believe, was of the lymphoblastic type. The surgeon did a total gastric resection and removed half the pancreas, all the regional lymph nodes and the spleen. The patient received x-ray treatment and went home; from what I gather she was still well six months later.

Dr. Alfred Kranes: Is that the treatment you would recommend for lymphoma—surgical removal?

Dr. Castleman: If lymphoma limited to one area, especially a part of the gastrointestinal tract, can be removed—and the surgeon thought it could all be removed en bloc in the patient under discussion—I believe that resection is worth while. Another reason for resection is that at operation the surgeon cannot be sure that the lesion is not a carcinoma; it may be difficult for the pathologist to differentiate a lymphoma and an anaplastic carcinoma on a frozen section.

Dr. Kranes: I thought you said the lymph nodes were also involved.

Dr. Castleman: Two nodules close to the stomach were involved. Whether they were lymph nodes or extension of tumor is difficult to decide. As far as the surgeons could tell, the disease was localized to the stomach and surrounding tissue.

Dr. Maloof: Would the surgeon have removed the spleen if he had known it was not involved?

Dr. Castleman: Yes; he would have had to remove it because he wanted to remove part of the body and tail of the pancreas.

A Physician: Is the prognosis better or worse with lymphoma of the stomach than with lymphoma of the mediastinum?

Dr. Castleman: It is much better. We have had at least half a dozen cases in which lymphoma localized to the gastrointestinal tract has been resected and the patient cured.

Dr. Wyman: May I put in a plug for x-ray treatment? This same sort of lesion has done well with radiation therapy in many cases.

Dr. Maloof: The Lahey Clinic[4] has had 8 patients with lymphoma of the gastrointestinal tract who have lived for five years after x-ray therapy alone.

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PHARMACEUTICAL FACT AND FANCY

The development of specific drug therapy during this century is a fact so firmly established that it makes the dramatic commonplace. Familiarity with the newer agents has bred not contempt but too often a casualness of attitude.

As therapy has become more precise, it has also become more dangerous. The Hippocratic principle, "First, do no harm," is still a sound guide. Too often is there an aggrieved response when drug cautions prove to have been justified. When clearly stated warnings are ignored, with dire results, an attitude of injured innocence is not warranted.

Lengthy and often costly research precedes the introduction of a new drug. The product is reviewed by the Food and Drug Administration. The judgment of the Council on Pharmacy and Chemistry of the American Medical Association is available when requested. A drug so processed and used according to the indications and cautions suggested by medical research and the reviewing authorities has been made as safe as its characteristics permit.

Ethical pharmaceutical firms are aware of their responsibilities. The promotion of a new drug is usually accompanied by extensive informational material. Among recently noted phrases are the following: "Prepared for distribution to the medical profession exclusively"; "This agent can cause toxic as well as therapeutic response"; "The usual precautions should be observed"; "Blood counts . . . to determine at the earliest possible moment whether blood dyscrasias are occurring"; "Physicians are urged to familiarize themselves thoroughly with the properties and proper usage of this potent new agent before prescribing it."

Even with proper usage of drugs there are cases of idiosyncrasy and hypersensitivity, which are often unavoidable, no matter what limitations and restrictions are imposed on the use of drugs. The most innocuous botanicals or synthetic organic chemicals will in some patients produce untoward reactions and, in a few cases, death. But to withhold or ban most such drugs would reverse medical progress and lead to the death of many patients who might have been saved by the proper use of the drug.

There has been a tendency in medical journals, at medical meetings and in the newspapers to give sharply critical attention to single case reports of untoward reactions to drugs. Unless these reports are carefully considered in context, including such data as the number of patients to whom the drug has been given, the amount prescribed and the number of lives saved, incorrect impressions are imparted to physicians and indirectly to the public.

There is danger in viewing case reports with alarm unless they are sufficiently broad in scope to include the indications, limitations and contraindications of the drug under criticism. The busy practitioner, with neither time nor facilities to evaluate the broader aspects of one of the newer agents, may be influenced to withhold the drug when it might be sound practice to administer it.

There is an unfortunate tendency among physicians to write to authorities urging that if these case reports of toxicity are representative, the offending drug be withdrawn. Such pressure tactics may influence authorities to yield to the articulate complaints rather than harkening to wiser, more experienced physicians, who know that any drug can harm some persons while saving thousands.

If the alarmist reports continue and increase, there is grave danger that some irresponsible popular publicists will pick up the cue. This in turn can lead to a serious situation in which public opinion levels against the medical profession the charge that it is killing patients by using or abusing powerful drugs.

The seriousness of even the relatively rare toxic reaction should not be shrugged off or minimized. The mortality of even the extremely rare reaction is 100 per cent for the patient and for his family.

The physician who fails to realize the possible dangers inherent in many therapies is irresponsible. Failure to adhere to the best knowledge of the art and science of medicine is poor medical practice. It is but one step removed from self-diagnosis and self-prescription.

There may be times and places where overzealous promotion of new pharmaceutical products is offensive. The furnishing of samples and "initial-dose" supplies may lead to injudicious or overzealous prescription. Where abuses exist, they should be eliminated.

The physician must be helped to a better understanding and better use of the new therapeutic agents at his disposal. Medical writing should clearly set forth the indications, specific ranges of use and dangers of the agents available. The doctor should prescribe a specific remedy for a specific purpose. He should know and anticipate the dangers. He should closely follow his patient.

The literature should not by innuendo invite distrust of medical research, of the Council on Pharmacy and Chemistry or of the Food and Drug Administration. The few inevitable cases of untoward reactions should not be magnified out of proportion. Frightening the physician or his patient away from the proper use of a drug can cause more harm than that occurring as a side effect of a drug when it is properly used.

STREPTOMYCIN AND DIHYDROSTREPTOMYCIN

In 1946 it was reported that streptomycin salts may be reduced to form corresponding dihydrostreptomycin salts; these were found to be more stable in alkaline solution and to have other desirable chemical properties.[1,2] Subsequent reports on the comparative activity of streptomycin and dihydrostreptomycin, both in vitro and in vivo, showed that the drugs were on the whole equally active, although against a number of bacterial species, including some strains of tubercle bacilli and of salmonella, dihydrostreptomycin was appreciably less active.[3,4]

In the November, 1948, issue of the *American Review of Tuberculosis* a series of six separate reports on laboratory and clinical aspects of dihydrostreptomycin appeared. Among them were two clinical reports, one on 14 patients treated at the Mayo Clinic and the other concerning 12 patients observed at the New York Hospital. The investigators in both clinics concluded that dihydrostreptomycin seemed to be as effective as streptomycin and had an advantage over the parent drug in being tolerated longer before toxic manifestations became apparent. The other important feature noted by the original observers was the fact that dihydrostreptomycin could be used to continue therapy in some patients who had shown sensitivity reactions to streptomycin. Although these workers were satisfied that dihydrostreptomycin represented a considerable improvement over streptomycin in this regard, both groups emphasized the fact that its administration in sufficiently large doses could produce the same type of damage to the nervous system as streptomycin. In addition a major drawback to large-scale use of streptomycin — the fact that strains of tubercle bacilli became resistant to the drug during treatment — was not overcome by the derivative; moreover, cross-resistance between the two agents was complete.

In spite of the small number of cases and the short period of study covered, these observations, the eminence of the investigators who reported them and the attending publicity and advertising given them by interested manufacturers had such a pre-

found effect on many, perhaps the great majority of, tuberculosis clinics and general hospitals that they rapidly turned from streptomycin to the use of dihydrostreptomycin. This shift reached such proportions that within a relatively short time nearly 90 per cent of all streptomycin that was produced and distributed was in the form of salts of dihydrostreptomycin.

It was not long, however, before workers began to realize that dihydrostreptomycin was by no means as innocuous as the early reports had led them to expect; indeed, it was soon found that its use was accompanied by potential toxicity fully as grave as that of streptomycin, if not more so. Although the toxic effects of dihydrostreptomycin on the vestibular apparatus were less than those of streptomycin, damage to the auditory nerve was far more frequent and more severe with dihydrostreptomycin. Permanent loss of hearing and even complete deafness were encountered all too frequently, particularly when intensive and prolonged therapy with the new derivative was employed.[6-7] These complications led several observers to decry the routine use of dihydrostreptomycin and to recommend its limitation to patients who had become sensitized to streptomycin.

An attempt at a more controlled study of the comparative toxicity and efficacy of the two forms of streptomycin was made by the workers in the various hospitals collaborating with the Veterans Administration's study on the chemotherapy of tuberculosis. Data in groups of patients treated in exactly the same manner but given either streptomycin or dihydrostreptomycin, the choice of agent being entirely by a random selection, were presented at the eleventh Conference on the Chemotherapy of Tuberculosis in January, 1952. The study indicated that dihydrostreptomycin and streptomycin were equally effective and in fact equally toxic, but whereas streptomycin was somewhat more toxic to the vestibular apparatus, dihydrostreptomycin caused more auditory damage and perhaps slightly fewer hypersensitivity reactions.

At the most recent of those conferences, held in February, 1953, Dr. Charles A. Light presented the results of another controlled study on the ototoxicity of these two agents conducted as a collaborative effort in several widely scattered independent sanatoriums. A total of 379 patients were given doses of 1 gm. daily for a hundred and twenty days, 189 receiving streptomycin sulfate and 190 dihydrostreptomycin sulfate. After a follow-up period of six months vestibular damage, both subjective and objective, was observed in 27.6 per cent of those receiving streptomycin and in 7.4 per cent of those who were given dihydrostreptomycin; auditory damage occurred in 6.3 per cent of the former and in 19.9 per cent of the latter.

Two additional studies dealing with the combined use of streptomycin and dihydrostreptomycin, one experimental and the other clinical, were reported at this conference. The laboratory study, by Poutsiaka, Thomas, Linegar and Hobson, dealt with ataxia in cats — a delicate test for vestibular function. The results of these tests showed that the time required for ataxia to develop in the cat from either streptomycin or dihydrostreptomycin was inversely related to the dose and that with the same dose it took appreciably longer to demonstrate ataxia with dihydrostreptomycin. When a similar total amount was used as a 1:1 mixture of the two agents, the appearance of ataxia was somewhat delayed (but not very much so) over the time required for it to appear when streptomycin alone was used. This finding, though by no means striking, was considered important enough to warrant clinical trial of the mixture.

Such a clinical trial was reported by Heck and Hinshaw in 110 patients, each of whom was given daily doses of 1 gm. for a hundred and twenty days; 34 received streptomycin, 34 dihydrostreptomycin, and 42 the 1:1 mixture of the two agents. The occurrence of vestibular and auditory damage was studied during a six months' follow-up period. Vestibular disturbances were noted in 6 (18 per cent) of patients treated with streptomycin and in 2 (6 per cent) of those receiving dihydrostreptomycin; auditory disturbances were noted in none of the former, and in 5 (15 per cent) of the latter. All the 42 patients treated with the 1:1 mixture remained free of both vestibular and auditory disturbances.

Although this clinical demonstration appears to be quite striking, and indeed is already being exploited, it seems wise, in view of the earlier experiences, to accept the conclusions with caution and reserve. In the first place, the number of patients was not large, and the results, judging from the laboratory experiment, appear to have been inordinately favorable. Further observations in large numbers of cases are certainly necessary to ascertain whether equally favorable results can be obtained regularly, and under other circumstances — for example, under different treatment regimens.

It is essential to bear in mind that, in spite of the recent introduction of isoniazid and the demonstration of its effectiveness in tuberculosis, streptomycin, either as such or as dihydrostreptomycin is still the mainstay of long-term antituberculosis therapy. Perhaps the most critical situation in which the availability of the two forms of streptomycin has proved useful is in patients who have become sensitized to one or the other of these agents; in such patients it has been possible to give the alternate compound and continue therapy without serious reactions and thus permit the prolonged therapy that has proved so desirable and necessary. The possibility of sensitizing patients to both agents is certainly a hazard to be seriously considered and weighed.

In addition, daily doses of streptomycin were used in the study by Heck and Hinshaw and in the one reported by Light, perhaps deliberately for the purpose of obtaining effects that could be compared. Such doses are no longer considered necessary or desirable except possibly for short periods when chemotherapy is being instituted in acutely ill patients or in preparation for surgery. The more desirable and acceptable regimen for the great majority of patients, at least for purposes of long-term therapy when the neurotoxicity of streptomycin is most important, employs streptomycin only twice a week in conjunction with para aminosalicylic acid daily; with this regimen the incidence of both vestibular and auditory disturbances from either form of streptomycin is low. This removes another impelling cause for seeking to confuse chemotherapy by the use of multiple combined agents, each of which has certain distinct properties that it may be desirable to invoke separately in critical situations.

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PRIZE-ESSAY AWARDS

THE *Journal* takes pleasure in again reporting the results of its student prize-essay competition and in publishing at the same time the prize-winning essay. This fifth in the series of annual contests was also the one most widely participated in, and a number of creditable case reports were received.

A majority of the judges agreed that "Malignant Thymoma in Myasthenia Gravis: Report of an unusual case, with a brief discussion of the role of the thymus in the disease," by Jay Harris Katz, a fourth-year student at Harvard Medical School, seemed to be of the highest merit, and Mr. Katz was awarded the first prize of $100. His essay appears elsewhere in this issue of the *Journal.*

Because of the generally high quality of the papers submitted, two "consolation" prizes were awarded this year, instead of one. Thomas H. Hindle, III, of Temple University School of Medicine, received the second prize of a two-year subscription to the *Journal* for his report of a case of "Xanthoma Disseminatum with Diabetes Insipidus," and George C. Glenner, of Johns Hopkins University School of Medicine, was awarded third prize of a one-year subscription for a case record and discussion of "Syphilitic Coronary Ostial Disease."

At this time a reminder to present third-year students that the *Journal* plans a similar contest for 1954 may be in order. As before, it will consist of the report of a case that the student has personally studied, with a discussion and review of the subject. But of this more anon.

Eccentricities of Medical Men —

"For physic and farces
Their equal there scarce is; —
Their farces are physic,
Their physic a farce is."

Boston M. & S. J., *June 22, 1853*

MASSACHUSETTS MEDICAL SOCIETY

ANNUAL GOLF TOURNAMENT

The winners at the annual golf tournament of the Massachusetts Medical Society, held at the Wollaston Golf Club on the afternoon of Wednesday, May 20, were as follows: low gross, Dr. Joseph Hammer, of Wellesley; second low gross, Dr. Francis J. Wenzler, of Mattapan; low net, Dr. Roy J. Heffernan, of Brookline; and second low net, Dr. George R. Gagliardi, of Framingham.

DEATH

FITZ — Reginald Fitz, M.D., of Brookline, died on May 27. He was in his sixty-ninth year.

Dr. Fitz received his degree from Harvard Medical School in 1909. He was assistant dean and lecturer on the history of medicine at Harvard Medical School. He was a former member of the staffs of Massachusetts General, Johns Hopkins and Peter Bent Brigham hospitals and of the Mayo Clinic, and was a fellow of the American Medical Association, serving on its council of education and hospitals. Dr. Fitz was formerly chairman of the American Board of Internal Medicine, president of the Massachusetts Medical Society and president of the Suffolk District Medical Society. He was also a member of the Academy of Arts and Sciences, the Association of American Physicians, the American Society for Clinical Investigation, the Massachusetts Heart Association and the Boston Tuberculosis Society, and was past president of the American College of Physicians.

He is survived by his widow, three daughters and two sons.

CORRESPONDENCE

"QUECKSILBER"

The article, "Medicine and the Doctor in Word and Epigram" by Dr. Sara M. Jordan in the May 21 issue of the *Journal* was both interesting and stimulating; it is fascinating to see how a single word may, at times, condense centuries of history.

Thus, the article asserts that the word "quack" originated with the Danish *Kwakzalver* ("one who boasts of his salves"). My understanding of the derivation of this word, although possibly mistaken, is somewhat different.

In the sixteenth century, mercury inunction of skin lesions was a popular treatment for syphilis; the German word for mercury is *Quecksilber*, and that for salve, *Salbe*. Practitioners of this treatment were accordingly called *Quecksalber*, a contraction of *Quecksilber* and *Salbe;* later on, the spelling changed to *Quacksalber*, and it may have been at that point that the word was introduced into the Danish language.

Since mercury inunction not only was unsuccessful but also produced painful and extensive cutaneous exfoliation, it is not surprising that the original meaning of the word soon changed to mean boastful and fraudulent treatment ("Quacksalberei").

THOMAS ROBITSCHER

Boston University School of Medicine

Note: Neither the *Oxford English Dictionary* nor Webster's *New International Dictionary* confirms the tempting bit of etymology offered by Mr. Robitscher: the former gives the derivation as "early mod. Du. (16th c.) *quacksalver* . . ., whence also G. quacksalber . . ." and the latter as "D., now *kwakzalver*; cf D. *kwakzalven* to quack or boast one's salves." — ED.

BOOK REVIEWS

Treatment of Mental Disorder. By Leo Alexander, M.D. 8°, cloth, 507 pp., with 143 illustrations. Philadelphia: W. B. Saunders Company, 1953. $10.00.

This new textbook is good therapy for the present-day "schizophrenia of psychiatry," which is generally thought of as divided into two separate fields, the mental and the physical, to which either an "organic" or a "psychologic" approach is applied. In this book, however, the results of insulin coma, electroshock and psychosurgery and those of psychotherapeutic measures are interpreted and explained in terms of each other; thus, for the first time, a clear-cut explanation of how physical treatment influences the psychic state of the patient is offered. At the same time, it examines fully many of the basic humanistic problems in psychiatry that some writers prefer to ignore. This is a unique work; there has been no book like it in the past twenty years. In fact, it contains all that can be said about neuropsychiatry up to 1953.

The introductory chapters provide a basic orientation in the nature of mental disorder. Well chosen case histories demonstrate the many factors involved and show clearly how even such indisputably physical predisposing factors as body type may have not only physical but also psychologic meaning. The author emphasizes the importance of a carefully defined, soundly determined social attitude toward the treatment of mental illness. He includes for consideration the important fact that decisions about the treatment of mental illness rest with the next of kin or legal guardian and not with the patient himself.

The chapter on general principles of psychotherapy will bring every reader up to date in this important area. The chapter on general principles of physical treatment by shock, stimulation and by psychosurgery emphasizes the enormous recent advances made in these types of treatment. Special chapters are also devoted to the treatment of alcoholism and states of intoxication caused by other toxic substances. Especially interesting is the section dealing with treatment of the new nerve gases, which may become an important issue in the event of another war.

The unique feature of this book is that it gives precise information about treatment; it tells the physician what to do and what not to do. It elucidates in detail all standard elements of psychotherapy in their nonverbal as well as their verbal aspects. Outstanding in its originality and clarity of presentation is the section dealing with convulsive and nonconvulsive electroshock, containing diagrams and detailed step-by-step directions. These discussions of practical technic will be particularly helpful to those doctors who are embarking on work in mental hospitals and to the medical student who is just becoming familiar with the various aspects of treatment. Moreover, a special chapter is devoted to the ways in which the nurse can co-operate most fully with the doctor and thereby facilitate the course of psychiatric therapy; this section is clearly presented in language that the average nurse can understand.

Every psychiatrist, regardless of his orientation or training, can find in this book some fresh information or new point of view. It includes broadly the psychoanalytic point of view but is not limited by it. Rather, it treats of mental disorder as a basic section of human illness and includes social and cultural factors as fundamental to the understanding and treatment of mental disorder.

MERRILL MOORE, M.D.

Salud y libertad: Oraciones de un creyente. By Prof. Dr. Carlos Enrique Paz-Soldan. 8°, paper, 351 pp. Lima, Peru: Biblioteca de Cultura Sanitaria, 1953.

The author, who is professor of Hygiene at the University of Lima and a well known historian, has reprinted his own papers on social medicine and those of others, covering the period of the last three decades. Health is considered from the points of history, politics, economics, ethics, freedom of speech and publications. Extracts from the works of Rodriquez, Masaryk, Jefferson and others are included. The volume marks the twenty-fifth anniversary of the Institute of Social Medicine at the University of San Marcos in Lima.

HENRY R. VIETS, M.D.

Childhood Experience and Personal Destiny. By William V. Silverberg, M.D. 8°, cloth, 289 pp. New York: Springer Publishing Company, Incorporated, 1952. $4.50.

This book represents the efforts of a psychoanalyst of thirty years' experience to draw closer together the psychologies of Freud and Harry Stack Sullivan.

In the first section the author discusses in concise terms the basic concepts of both men, as well as their differences. He shows how they overlap to a considerable extent. Freud put most emphasis on the id or unconscious processes, and Sullivan was mainly concerned with ego growth and the effect of interpersonal relations on its development. The author believes that the framework or foundation of the personality is laid down during the first five or six years of life. Although he recognizes the importance of environmental factors, he believes that this fundamental personality structure is utilized in adaptation throughout life. He breaks down the early periods in personality development in a slightly different fashion from that of Freud and, in doing so, broadens the areas in the growth period and encompasses a larger variety of situations in each area.

In the oral phase, he discusses problems of deprivation associated with nursing and weaning.

In the anal period, he discusses not only the problems of toilet training per se but also those of the various experimental areas in which discipline becomes a factor in the child's growth. He demonstrates how other forms of discipline may precede actual toilet training, especially if the parents are somewhat permissive in this function.

During the phallic phase, he brings out the problems of rivalry in the family as well as the increased genital awareness in relation to others in the environment. He thinks that the so-called "latency period" is not universally found but may develop in certain restrictive middle-class environments.

The origins of homosexuality are discussed at considerable length as one of the pathologic resolutions of the Oedipus situation.

The author concludes the book with a section on psychotherapeutic aims. His concept of mental health, as the end desired in psychotherapy, embraces the following qualities:

> Competence in dealing with familiar situations; courage and resourcefulness in meeting new ones; the wisdom and humility to know one's powers and their limitations. Mental health seems to equate with qualities of maturity: reliable competence as distinguished from occasional flashes of cleverness and brilliance; persevering courage as distinguished from rashness and bravado; and humble wisdom as distinguished from arrogant ambition and intellectual conceit.

In the reviewer's opinion, this book offers much to the worker in the field of mental health in that the author builds the foundation of dynamic personality development in clear and ordered fashion and, at the same time, gives a greater insight into the unconscious mechanisms involved in all interpersonal situations as they occur in present culture.

JOHN B. HAYES, M.D.

The Love and Fear of Flying. By Douglas D. Bond, M.D. With a preface by General H. Doolittle. 8°, cloth, 190 pp. New York: International Universities Press, Incorporated, 1952. $3.25.

Dr. Bond has written an interesting book. It deals in a forthright manner with the problems and fears of flying personnel. It specifically deals with the case study of flyers in the training command of the United States Air Force and the Eighth Air Force stationed in England during World War II. The book considers anxiety states of flying personnel, as well as the causes, and briefly outlines treatment as used by the Eighth Air Force.

Of particular interest is the chapter entitled "Diagnosis and Administrative Policy." In this chapter, Dr. Bond points out that "the physician was the subordinate of Command, and Administrative Policy played an overwhelming role in determining treatment, the use of men incompetent through illness, and even diagnosis itself."

The undersigned served as a psychiatrist and flight surgeon to the Twentieth Air Force in the Pacific and encountered many of the problems outlined in this chapter. The rate of emotional disorders in very-heavy-bombardment crews in the Pacific, however, was associated not only with the combat danger itself but also with the long over-water flights to the Japanese Empire and the ever-present anxiety of ditching.

Dr. Bond's book should be of interest and service to psychiatrists, especially to those associated with flying personnel. Flight surgeons will find answers to some of their most perplexing problems.

The book is useful and stimulating, and is written in a clear and concise manner.

RONALD H. KETTLE, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Helping Parents Understand the Exceptional Child: "The cornerstones of understanding." Proceedings of the Annual Spring Conference on Education and the Exceptional Child under the Auspices of the Child Research Clinic of the Woods School at Langhorne, Pennsylvania. 8°, paper, 42 pp. Langhorne, Pennsylvania: The Woods Schools, 1952. No charge.

In this small pamphlet there are six articles on the psychology of the exceptional child, including one by Dr. Leo Kanner, entitled "The Emotional Quandaries of Exceptional Children."

The Principles and Methods of Physical Diagnosis: Correlation of physical signs with physiologic and pathologic changes in disease. By Simon S. Leopold, M.D., associate professor of clinical medicine, and director of the teaching of physical diagnosis, University of Pennsylvania School of Medicine, and chief of the Thoracic Clinic, Hospital of the University of Pennsylvania. With a chapter on "Sounds from the Thorax: Acoustic principles," by S. Reid Warren, Jr., Sc.D. in E.E., professor of electrical engineering, Moore School of Electrical Engineering, University of Pennsylvania. 8°, cloth, 430 pp., with 390 illustrations with 19 color plates. Philadelphia: W. B. Saunders Company, 1952. $7.50.

This new book has been written primarily for students, and as the title indicates, the author has concentrated on the correlation of physical signs with physiologic and pathologic changes in disease. The material is arranged by regions and systems of the body. References are given when considered pertinent. There is a good index, and the publishing is excellent.

Transactions of the American College of Cardiology: Volume I — 1951. Editor, Bruno Kisch, M.D. 8°, paper, 138 pp., with illustrations. New York: American College of Cardiology, 1952.

This volume contains the papers read at the first meeting of a new society held in New York on October 6, 1951. An obituary of Dr. Franz M. Groedel (1881-1951), the first president, and the constitution and by-laws of the College precede the papers. It is planned to issue a volume annually. The series should be in all medical libraries.

Manual of Gynecology. By E. Stewart Taylor, M.D., professor of obstetrics and gynecology and head, Department of Obstetrics and Gynecology, University of Colorado School of Medicine. 8°, cloth, 204 pp., with 70 illustrations. Philadelphia: Lea and Febiger, 1952. $4.50.

Dr. Taylor has written this manual for the purpose of providing medical students and the general practitioner with the basic essentials of gynecology. The whole field of the subject is covered, and lists of references are appended to the chapters. There is a good index, and the publishing is excellent.

(*Books Received concluded on page xv*)

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4. Kagan, B.M., et al.: Polymyxin B and Polymyxin E, J. Lab. & Clin. Med. *37*:402, 1951.
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BOOKS RECEIVED (*Concluded from page 1080*)

Post-Operative Care. By H. J. B. Atkins, D.M., M.Ch.(Oxon.), F.R.C.S.(Eng.), surgeon and director of the Department of Surgery, Guy's Hospital. Fourth edition. 8°, cloth, 338 pp., with 64 illustrations. Springfield, Illinois: Charles C Thomas, 1952. $6.75.

Dr. Atkins has revised the text of his fourth edition to bring it up to date. The chapter on antibiotics has been thoroughly revised, and the chapter on fluid administration has been wholly recast. The arrangement of the material is excellent, covering the various systems and organs of the body, with chapters on rehabilitation and operations on children. The printing was done in Great Britain, and the publishing is excellent. This special book should be in all surgical collections.

NOTICES

SOCIETY MEETINGS AND CONFERENCES

JUNE 26-28. American Academy of Dental Medicine. Page 664, issue of April 9.

JUNE 28–JULY 2. American Society of X-Ray Technicians. Page 480, issue of March 12.

JULY 8-9. Seventh Annual Rocky Mountain Cancer Conference. Page 644, issue of April 9.

AUGUST 18-21. Third International Congress of Electroencephalography and Clinical Neurophysiology. Page 707, issue of April 16.

OCTOBER 19-30. New York Academy of Medicine. Page xvii, issue of June 11.

OCTOBER 28. New England Obstetrical and Gynecological Society. Page 868, issue of November 27.

DISTRICT MEDICAL SOCIETIES

MIDDLESEX SOUTH

SEPTEMBER 23.
NOVEMBER 18.
JANUARY 20. (Combined with the Auxiliary.)
MARCH 24.
MAY 12. Annual Meeting. (Harlow Dinner.)

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JUNE 25

THURSDAY, JUNE 25

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
9:00–10:00 a.m. Grand Rounds. Russell Room, House of the Good Samaritan.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

FRIDAY, JUNE 26

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
*10:00 a.m.–1:00 p.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:30–11:15 a.m. Diabetes Lecture. Dr. Elliott Joslin. New England Deaconess Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

SATURDAY, JUNE 27

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.
*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Blood Clinic. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, JUNE 29

*8:00–9:00 a.m. Combined Medical and Surgical Rounds for Diabetic Surgery Cases. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12-15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
5:15 p.m. Staff Meeting. Harris Hall, New England Deaconess Hospital.
*7:00–9:00 p.m. Anesthesia Teaching Conference. Stearns Auditorium, New England Center Hospital.

TUESDAY, JUNE 30

*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
*12:00 m.–1:00 p.m. Regular Grand Rounds of the Pediatric Department. Dowling Amphitheater, Boston City Hospital.
*12:00 m.–1:00 p.m. Pediatric Rounds, Burnham Memorial Hospital for Children, Massachusetts General Hospital.
*12:15–1:15 p.m. X-ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical), Faulkner Hospital.

WEDNESDAY, JULY 1

*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Medical Conference. (Children's Medical Center.) Jimmy Fund Building, 25 Binney Street.
12:30 p.m. Weekly Pathological Meeting. Joslin Amphitheater, New England Deaconess Hospital.
12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. (Children's Medial Center.) Jimmy Fund Building, 25 Binney Street.
*4:00 p.m. Thoracic Conference. Held by Overholt Clinic. Harris Hall, New England Deaconess Hospital.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.

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